Vitamin D and pregnancy outcomes: Overall results of the FEPED study

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Review

Alexandre J. Vivanti[1,*], Isabelle Monier[1,2], Eleonora Salakos[1], Caroline Elie[3], Vassilis Tsatsaris[4,12], Marie-Victoire Senat[5], Jacques Jani[6], Jean-Marie Jouannic[7], Norbert Winer[8], Jennifer Zeitlin[9], Charlotte Mougneaud[1], Jean-Claude Souberbielle[10], Marie Courbebaisse[11], Alexandra Benachi[1,12].

1) Service de Gynécologie-Obstétrique, Hôpital Antoine Béclère, Assistance Publique des Hôpitaux de Paris, Université Paris Saclay, Clamart, France
2) Université de Paris, CRESS, INSERM, INRA, Paris, France
3) URC/CIC Paris Descartes Necker Cochin, Hôpital Necker-Enfants maladies, Assistance Publique des Hôpitaux de Paris, Paris, France
4) Service de Gynécologie-Obstétrique, Hôpital Cochin Port Royal, Assistance Publique des Hôpitaux de Paris, Université Paris-Descartes, Paris, France
5) Service de Gynécologie-Obstétrique, Hôpital de Bicêtre, Assistance Publique des Hôpitaux de Paris, Université Paris Saclay, Le Kremlin Bicêtre, France
6) Department of Obstetrics and Gynecology, University Hospital Brugmann, Université Libre de Bruxelles, Brussels, Belgium
7) Département de Médecine Fœtale, Hôpital Armand Trousseau, Assistance Publique des Hôpitaux de Paris, Université UPMC-Sorbonne, Paris, France
8) Service de Gynécologie-Obstétrique, CHU de Nantes, CIC Mère enfant Nantes, NUN, INRA, UMR 1280, Phan, Université de Nantes, Nantes, France
9) Université de Paris, CRESS, INSERM, INRA, Paris, France
10) Laboratoire d'Explorations Fonctionnelles, Hôpital Necker-Enfants malades, Assistance Publique des Hôpitaux de Paris, Paris, France
11) Service de Physiologie-Explorations Fonctionnelles Rénales, Hôpital Européen Georges Pompidou, Assistance Publique des Hôpitaux de Paris, Université de Paris, INSERM U1151, Paris, France
12) Fondation PremUp, Paris, France; Department of Obstetrics, Cochin Hospital, AP-HP, Université René Descartes, Paris, France

Abstract

Vitamin D insufficiency is highly prevalent in children and adults including pregnant women. During pregnancy, maternal vitamin D insufficiency could increase risks of several pregnancy complications and adverse birth outcomes. The FEPED study was designed to assess the effects of maternal vitamin D status in the first trimester during pregnancy on risks of preeclampsia, gestational diabetes mellitus (GDM), preterm birth and small-for-gestational age (SGA) at birth. This observational prospective cohort included 3129 women with a singleton pregnancy between April 2012 and July 2014 in six maternity units in France and Belgium. The aim of this review is to summarize the results of the FEPED study. At the first trimester the mean 25(OH)D concentration was 21.9 ± 10.4 ng/mL and 25(OH)D concentration was <20 ng/mL in 46.5% of patients. After matching 83 cases of preeclampsia with 319 controls, a significant decrease in the risk of preeclampsia was associated with maternal vitamin D levels ≥ 30 ng/mL in the third trimesters (OR=0.34; 95% CI: 0.13-0.86. P=0.023). In the first trimester, the risk for preeclampsia was decreased in these patients, but did not achieve statistical significance (OR = 0.57 95% CI, 0.30-1.01; p=0.09). For the 250 cases with GDM matched with 941 controls, no linear relationship was found between GDM and 25OHD levels in the first trimester of pregnancy. Finally, 2813 pregnant women were included in analyses of risks of preterm and SGA birth. No association was found between low maternal vitamin D levels in the first trimester and the risks of preterm birth (aOR=1.53; 95% CI: 0.97-2.43) or SGA (aOR=1.07; 95% CI: 0.75-1.54). Further investigation is needed to understand the mechanisms behind the association between vitamin D and birth outcomes.

Keywords

Vitamin D, 25(OH)-vitamin D_3, preterm birth, preeclampsia, gestational diabetes, FEPED

6/6 keywords

Vitamin D plays a role in the homeostasis of many organs. It is particularly involved in calcium absorption, leading to skeletal calcium balance and bone maintenance. It has also been associated with immune system interaction: inhibition of B or T cell proliferation[1], induction of T cell regulation[2], effects on dendritic cells and monocytes. In addition to its protective effect against bone demineralization, vitamin D sufficiency is associated with a reduced risk of many chronic diseases including type 2 diabetes mellitus, cardiovascular diseases, cancers, auto-immune and infectious diseases[3]. Vitamin D status can be assessed by serum measurement of the serum concentration of 25(OH)-vitamin D (25(OH)D). According to the Endocrine Society Clinical Practice Guideline, vitamin D deficiency is defined as 25(OH)D below 20 ng/mL (50 nmol/L) and vitamin D insufficiency as 25(OH)D of 21–29 ng/mL (525–725 nmol/L)[4]. During pregnancy, the definition of vitamin D deficiency remains unclear[5]. It is admitted that vitamin D insufficiency among pregnant women is highly prevalent in most countries[6]: 18% percent of pregnant women in the United Kingdom, 25% in the United Arab Emirates and nearly 80% in the Netherlands have vitamin D levels less than 25 nmol/L[7].

The FEPED study was designed to assess the impact of maternal vitamin D status in the first trimester on the risks of preeclampsia (primary outcome). This observational prospective cohort included 3129 women with a singleton pregnancy between April 2012 and July 2014 in five maternity units in France (Béclère, Bicêtre, Cochin, Trousseau and Nantes university hospitals) and one in Belgium (University Hospital Brugmann). Inclusion criteria were women aged over 18 years, singleton pregnancies, gestational age ranged from 10 to <15WG at enrollment and having a healthcare coverage. The exclusion criteria were hypercalcemia (>2.65 mmol/L), high blood pression (>140/90 mmHg), renal failure

(creatinine > 120 µmol/L), bone disease, lithium therapy, bowel malabsorption and kidney stones disease. Maternal vitamin D levels were assessed at three points of pregnancy: in the first trimester (between 10 and 14 weeks), in the third trimester of pregnancy and at birth (at cord blood). The aim of this ~~review~~ article is to summarize the results of the FEPED study regarding the potential links between vitamin D levels and previously described major obstetrical issues.

Vitamin D levels throughout pregnancy among women of the FEPED cohort

Several international guidelines recommend vitamin D supplementation during pregnancy[8–10]. However, most of these studies focused on first trimester vitamin D levels. Vitamin D levels throughout pregnancy (first and third trimester) and at delivery (cord blood) were studied in the FEPED cohort[11]. This study assessed the vitamin D status of the French pregnant women and their newborns and the impact of the French guidelines regarding recommended vitamin D supplementation during pregnancy (cholecalciferol 100 000 IU administered in the 6th month of pregnancy)[12]. A total of 2803 women were included in this analysis. Vitamin D status was below 20 ng/mL in 46.5% of pregnant women in the first trimester of pregnancy. 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.

The recommended supplementation, which was received by 88.6% of participants, had a significant impact on serum vitamin D levels during the third trimester (32.5 ± 11.4

ng/mL in supplemented women versus 25.8 ± 11.4 ng/mL in non-supplemented women, p<0.001). However, 25(OH)D levels in cord blood, reflecting the vitamin D status of newborns[13], was only marginally higher in case of supplementation (17.2 ± 7.2 ng/mL versus 15.5 ± 7.1 ng/mL, p<0.01). Importantly, the FEPED study demonstrates that this high dose of cholecalciferol given once, 100,000 IU theoretically corresponding to 1100 IU daily during 3 months, is clearly insufficient to obtain serum 25(OH)D levels above 20 ng/mL in most newborns and is also insufficient to completely prevent severe vitamin D deficiency (defined as serum 25(OH)D concentration <10 ng/mL), which was present in 12.4% of newborns whose mothers had received the supplementation. In conclusion, vitamin D insufficiency is highly prevalent in the middle-north of France at the beginning of pregnancy and in cord blood, despite the recommended supplementation.

Preeclampsia

In France, prevalence of preeclampsia is around 0.5 to 7% of all pregnancies depending on maternal risk factors.[14],[15] Preeclampsia was defined as a blood pressure >140 mmHg or a diastolic blood pressure >90 mmHg and proteinuria >0.3 g/24h. This definition is the one currently used in France and it was also used internationally at the time of the FEPED study. Prevention of preeclampsia remains a cornerstone of therapeutic management because of its high morbidity and mortality and because there is currently no curative treatment. Several drugs and vitamin supplementations have been reported to reduce the incidence of preeclampsia. Vitamin D insufficiency in early pregnancy has been identified as an independent risk factor of preeclampsia.[16] In the study of Bodnar and colleagues in 274 women, serum 25(OH)D levels in early pregnancy were 15% lower in

women who developed preeclampsia compared with healthy controls. Furthermore, vitamin D insufficiency at less than 22 weeks of gestation was more prevalent among women who developed preeclampsia than among women who did not. Some studies suggest that sufficient vitamin D levels in early pregnancy may be protective against preeclampsia[17–19]. Others imply that normal levels in the second or mid-third trimester maintain the protective effect against preeclampsia[20,21]. The FEPED study explored the relationship between vitamin D insufficiency (defined as a serum 25(OH)D level below 30 ng/mL) in the first trimester (main outcome) and the occurrence of preeclampsia later in pregnancy[22]. A secondary objective was to evaluate the relationship between preeclampsia and vitamin D levels during the third trimester of pregnancy. Vitamin D insufficiency was defined as a serum 25(OH)D level below 30 ng/mL. The overall prevalence of preeclampsia was 3% (mean term at the onset of preeclampsia was 36.2 ± 3.8 weeks of gestation and nine cases before 32 weeks of gestation). Eighty-three cases of preeclampsia were matched to 319 controls randomly selected in a 1:4 ratio (**table 1**). In the first trimester, the risk for preeclampsia decreased in women with vitamin D sufficiency, but did not achieve statistical significance (OR=0.57 95% CI, 0.30–1.01; p=0.09). ~~The overall prevalence of preeclampsia in this cohort was 3.0%. Nine cases of preeclampsia occurred before 32 weeks of gestation.~~ The probability of preeclampsia decreased with the increase of 25(OH)D levels in the first trimester of pregnancy. For each 10 ng/mL increase, the risk of preeclampsia decreased by 19%, without however achieving statistical significance. In the third trimester, the risk for preeclampsia decreased in women with vitamin D sufficiency (OR = 0.43 95% CI, 0.23–0.80; p=0.008). In the first trimester, the risk for preeclampsia was decreased in these patients, but did not achieve statistical significance (OR = 0.57 95% CI, 0.30-1.01; p=0.09). The mean 25(OH)D level was significantly higher in controls compared with women with preeclampsia

(30.8 ± 11.0 vs. 27.7 ± 12.2 ng/mL; $p < 0.05$). Finally, vitamin D sufficiency at the first and third trimesters had a protective effect against preeclampsia compared with women with 25(OH)D < 30 ng/mL in both the first and third trimesters (OR = 0.34; 95% CI, 0.13-0.86; p=0.023).

In order to assess the interactions between vitamin D status and the pathogenesis of preeclampsia, global gene expression profiling was proposed[23]. The aim of this study was to identify vitamin D gene signatures related to preeclampsia during early pregnancy (transcriptomic analysis). A gene expression analysis was performed among pregnant women with 25(OH)D sufficiency and insufficiency. A set of vitamin D–associated genes related to preeclampsia was identified. Most of the dysregulated genes were associated with immune and inflammatory pathways (eg., downregulation of IL-10, which is already known to be decreased in the serum and placenta of women with preeclampsia).

A recent Cochrane meta-analysis including four randomized trials for a total of 499 women concluded that vitamin D supplementation may reduce the risk of preeclampsia compared to no intervention or placebo (RR 0.48, 95% CI 0.30 to 0.79)[24] ~~(table 2)~~. Although there is an association between 25(OH)D levels and the risk for preeclampsia, timing of vitamin D supplementation remains controversial. Vitamin D supplementation (4400 IU/day or 400 IU/day) initiated in weeks 10–18 of pregnancy failed to reduce the incidence of preeclampsia.[23] However, women with sufficient first-trimester levels of 25(OH)D (≥30 ng/mL) had lower rates of preeclampsia. In France, vitamin D supplementation is recommended with 100,000 IU of cholecalciferol administered at month 7 of gestation. This strategy of vitamin D supplementation at the middle of the second trimester should be

questioned because i) sufficient levels of 25(OH)D seem to be needed in the first trimester to improve placentation and reduce the risk of preeclampsia and ii) although sufficient levels of 25(OH)D seem also to be needed at the third trimester, the results from the FEPED study have shown that this supplementation is insufficient to achieve serum 25(OH)D levels ≥30 ng/mL in nearly half of the women at the third trimester (vitamin D sufficiency was reported in only 58.2% of the supplemented women)[11]. For instance, the WHO does not yet support a policy of systematic vitamin D supplementation during pregnancy to improve maternal and perinatal outcomes[25]. Studies aimed at evaluating vitamin D supplementation from early pregnancy and even before pregnancy in at-risk women should be undertaken.

Gestational diabetes mellitus

Attempts to assess a potential link between 25(OH)D insufficiency and gestational diabetes mellitus (GDM) have been made for many years. Studies of an Iranian cohort and of an Australian cohort suggested an inverse correlation between maternal 25(OH)D levels during the mid-second trimester and the incidence of GDM[26,27]. Lu and colleagues published a large meta-analysis including a total of 20 observational studies and 16,515 pregnant women (cohort, cross-sectional, case control or nested case control)[28]. The authors showed that 25(OH)D insufficiency during pregnancy was associated with increased GDM risk (RR 1.45; 95% CI 1.15–1.83; $p<0.001$). Most of their findings were consistent with the findings of previously reported observational studies, however substantial heterogeneity was detected across the studies included (I^2 = 67%; $p<0.001$). Most studies included were cross-sectional, with small sample, different cut-offs and lack of adjustments for confounding factors. Because of such heterogeneity, a subgroup analysis was performed. It

seems that the link between 25(OH)D insufficiency and GDM was still present if the studies were performed in developed countries. Taken together, their results should be viewed with caution because of the low quality of several of the studies included. Similar results were also found in two previous meta-analyses in which low concentrations of 25(OH)D increased the risk of GDM in nearly 50% of cases[29,30]. Data extracted from the FEPED study were analyzed to assess the risk of GDM according to 25(OH)D concentration during the first trimester of pregnancy[31] (**table 1**). Cases of GDM were matched to eligible controls randomly selected in a 1:4 ratio. The overall rate of GDM was 8.3% in the FEPED cohort: 250 cases were matched with 941 controls. The risk of GDM was higher among women with 25(OH)D ~~insufficiency~~ defficiency below 20 ng/mL at the first trimester (OR=1.42; 95% CI 1.06-1.91; p=0.02). However, this association was no longer significant when modifying the cut-off to consider 25(OH)D insufficiency.

The latest Cochrane meta-analysis also evaluated the impact of systematic vitamin D supplementation on the risk of GDM[24] ~~(**table 2**)~~. Four RCT's were included (446 pregnant women). Vitamin D supplementation was considered as a protecting event (RR 0.51 95% CI 0.27-0.97) with a moderate certainty of evidence according to GRADE methodology. Taken together, the evidence in the literature suggests that low 25(OH)D status in the first trimester of pregnancy may increase GDM risk. However, the use of different thresholds in literature reports suggests that the strength of the link between 25(OH)D concentration and the risk of GDM should be questioned.

Preterm birth

Vitamin D may play a role in the prevention of infections. Low levels of 25(OH)D seem to be associated with bacterial vaginosis during pregnancy[32], which is known to be a risk factor for preterm rupture of membranes. Several studies have therefore suggested that vitamin D supplementation during pregnancy could reduce the risk of preterm birth, but the results differ between studies. A large observational cohort supports the idea of a protective effect of vitamin D sufficiency on preterm birth[33], but those results are counterbalanced by other observational studies[34–36]. The FEPED study evaluated the association between maternal 25(OH)D levels in the first trimester of pregnancy and the risk of preterm birth[37] (**table 1**). A total of 2813 women were included. Forty-five percent of pregnant women had a serum 25(OH)D concentration below 20 ng/mL and 27% lower than 15 ng/mL in the first trimester (1st quartile). Low 25(OH)D concentrations were associated with obesity, ethnicity, skin color and season at blood sampling. Nearly 7% of the women included experienced a preterm birth. Logistic regression was used to estimate adjusted odds ratios (aOR) for preterm birth. OR were adjusted on maternal age, parity, BMI before pregnancy, medical or obstetrical history, smoking, ethnicity, skin color and season at blood draw. For the risk of preterm birth, the adjusted odds ratio associated with 25(OH)D concentrations below 15 ng/mL (first quartile of 25(OH)D levels) was 1.53 (95% CI 0.97-2.43) in the whole population compared to the fourth quartile (30+ ng/mL). Analyses stratified by skin color found that dark-skinned women with low 25(OH)D levels in early pregnancy had a higher risk of preterm birth (aOR=2.89, 95% CI 1.02-8.18) compared to those with higher 25(OH)D levels. No association was found in women with lighter skin. These results are concordant with a previous study in the USA stratified by ethnicity which showed protective effects of vitamin D for spontaneous preterm births among black women, but not white women[38].

A recent Cochrane meta-analysis of seven randomized trials including a total of 1640 women ~~(table 2)~~ found that vitamin D supplementation may not reduce the risk of preterm birth compared to no intervention or placebo (RR 0.66, 95% CI 0.34 to 1.30). It is important to note that the numbers of women included differed greatly from one trial to another (from 19 to 486) and the baseline characteristics could have been different from one trial to another (in particular, baseline concentration of 25(OH)D).

Small-for-gestational age

Vitamin D could play a role in the regulation of genes involved in trophoblast invasion and in angiogenesis for placenta implantation, which could impact fetal growth. Several observational studies have suggested an association between low 25(OH)D levels in early pregnancy[39,40] and the second trimester[41] and a higher risk of SGA at birth for Caucasian women. However, this difference no longer remained significant for African women[41]. In the FEPED cohort, 336 women (11.9%) had an SGA neonate (birthweight <10th percentile for gestational age). No association was found between low maternal 25(OH)D levels in the first trimester of pregnancy and the risk of SGA at birth in the overall sample using clinical cut-offs and quartiles (respectively: aOR=1.10, 95% CI 0.80-1.52 for 25(OH)D levels <20 ng/mL and aOR=1.07, 95% CI 0.75-1.54 for 25(OH)D levels <15 ng/mL (first quartile) compared to the fourth quartile). Similar results were found for analysis stratified by skin color.

The impact of vitamin D supplementation has been questioned by several authors. A meta-analysis published in 2015, which included three RCT's (between 1980 and 2014) and 232 patients, did not suggest any association between vitamin D supplementation and risk for low birthweight (under 2500g)[42]. This meta-analysis was counterbalanced by another meta-analysis[43] which pooled 741 women of five RCT's and concluded that vitamin D supplementation could help prevent SGA birth (RR=0.60, 95% CI 0.40-0.90, I^2=0%). The latest Cochrane meta-analysis evaluated the risk of low birthweight (under 2500g) and included 697 women from five trials[24] ~~(table 2)~~. The authors concluded that systematic vitamin D supplementation could help reduce the risk of low birthweight compared to no intervention or placebo (RR=0.55, 95% CI 0.35-0.87, I^2=36%).

Conclusion

The FEPED study has highlighted that 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. In this study, a significant decrease risk of preeclampsia was associated with maternal serum 25(OH)D concentrations ≥ 30 ng/mL in the first and third trimesters (OR=0.34; 95% CI: 0.13-0.86. p=0.023). No linear relationship was found between GDM and 25(OH)D levels in the first trimester of pregnancy since GDM risk does not continuously decrease as 25(OH)D concentrations increase. Finally, no association was found between low maternal 25(OH)D levels in the first trimester and the risks of preterm birth (aOR=1.53; 95% CI: 0.97-2.43) or SGA (aOR=1.07; 95% CI: 0.75-1.54). However, subgroup analyses showed that women with darker skin color and lower 25(OH)D levels had an increased risk of preterm birth (aOR=2.89; 95% CI: 1.02-8.18 in the first quartile (<15 ng/mL) compared to the fourth quartile (30+ ng/mL).

FEPED is the first European study who explicitly assessed the effects of maternal 25(OH)D status throughout pregnancy on birth outcomes. Maternity units were at similar latitudes limiting variability in sun exposure and 25(OH)D blood was measured at three cut points of pregnancy: in the first trimester of pregnancy (10-14 weeks), during the third trimester and at birth (cord blood sampling). Additionally, strengths of the study were the large sample of women, data collected on skin color using the Fitzpatrick scale and the few missing data.

However, the FEPED study has several limitations. The first include its observational design, which means it is not possible to demonstrate a causal relationship. For the preeclampsia and GDM case-control study, which was nested in a large cohort, each case was paired with controls according to known risk factors of these diseases (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). Although all precautions were taken in matching cases with controls, it cannot be excluded that some unknown confounding factors could have introduced a bias, even after matching for known risk factors. Moreover, the potential for residual confounding remains and, in particular, the mother's socioeconomic characteristics were not considered, but are known to be linked to preterm birth and SGA at birth.

The literature regarding potential links between 25(OH)D concentrations and/or Vitamin D supplementation during pregnancy is controversial because of a very high heterogeneity in observational studies, trials and meta-analyses. Aggregated evidence suggests that some differences can depend on the populations studied, including skin phenotype, nutrition, physical activity and place of residence (latitude). Moreover, several studies have been compared and pooled but differ on many points: baseline levels of 25(OH)D, timing of supplementation, cut-offs set to define vitamin D insufficiency, technical measurement of 25(OH)D concentrations, and so forth. Taken together, the conclusions of most studies should be considered in light of the low grade of evidence. However, according to the biological functions of vitamin D and the literature analysis, 25(OH)D levels and/or vitamin D supplementation may interact with the risks of preeclampsia and GDM. Rigorous

and high-quality randomized prospective trials should be started to solve all the mysteries of vitamin D and its interaction with major obstetrical issues.

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Table 1: Summary of the obstetrical outcomes according to the FEPED observational cohort

Risk	**Prevalence**	**25(OH)D levels (ng/mL) 1st trimester cases**	**25(OH)D levels (ng/mL) 1st trimester controls**	**p**	**25(OH)D insufficiency <30 ng/mL 1st trimester - cases**	**25(OH)D insufficiency <30 ng/mL 1st trimester - controls**	**OR [95% CI]**	**p**
Preeclampsia	3.0% (84/2797)	20.1 ± 9.3	22.3 ± 11.1	0.09	83.1% (69/83)	74.0% (236/319)	0.57 [0.30-1.01]	0.09
Risk	**Prevalence**	**25(OH)D levels (ng/mL) 1st trimester cases**	**25(OH)D levels (ng/mL) 1st trimester controls**	**p**	**25(OH)D ~~insufficiency~~ defficiency <20 ng/mL 1st trimester - cases**	**25(OH)D ~~insufficiency~~ defficiency <20 ng/mL 1st trimester - controls**	**OR [95% CI]**	**p**
Gestational diabetes	8.3% (258/2690)	21.1 ± 10.0	22.7 ± 10.0	0.03	50% (125/250)	41.9% (394/941)	1.42 [1.06-1.91]	0.02
Risk	**Prevalence**				**25(OH)D ~~insufficiency~~ defficiency <15 ng/mL 1st trimester**	**25(OH)D ~~insufficiency~~ defficiency <15 ng/mL 1st trimester**	**aOR [95% CI]**	
Gestational age at birth	6.7% (189/2813)				**<37 weeks** 34.4% (65/189)	**≥37 weeks** 26.6% (698/2624)	1.53 [0.97-2.43]	
Birthweight (<10th percentile)	11.9% (336/2813)				**<10th percentile** 27.4% (92/336)	**≥10th percentile** 7.0% (669/2477)	1.07 [0.75-1.54]	

Table 2: Obstetrical outcomes regarding vitamin D supplementation for women during pregnancy (adapted from Palacios et al, Cochrane Database of Systematic Reviews 2019)

Risk	**Total events Group vitamin D**	**Total events Placebo group/no supplementation**	**Relative risk (95% CI)**	**Heterogeneity I^2 - p**	**Quality of the evidence (GRADE)**	**Studies included**
Preeclampsia	7.7% (21/273)	16.8% (38/226)	0.48 (0.3 0.79)	I^2=0% - p=0.91	Moderate	[44,45,56,57]
Gestational diabetes	5.2% (13/249)	12.7% (25/197)	0.51 (0.27 0.97)	I^2=0% - p=0.53	Moderate	[44–47]
Preterm birth	4.0% (34/856)	6.0% (47/784)	0.66 (0.34 1.3)	I^2=45% - p=0.1	Low	[44,48–52]
Low birthweight (<2500g)	10.7% (39/366)	21.1% (70/331)	0.55 (0.35 0.87)	I^2=36% - p=0.18	Moderate	[45,52–55]

Declaration of interests

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.