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Exploring the concept of functional vitamin D deficiency in pregnancy: impact of the interaction between 25-hydroxyvitamin D and parathyroid hormone on perinatal outcomes

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Short running head: Vitamin D, parathyroid hormone and pregnancy

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Trial registration: The SCOPE pregnancy cohort is registered at the Australian, New Zealand Clinical Trials Registry (http://www.anzctr.org.au), ID: ACTRN12607000551493.

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BP, blood pressure; LC-MS/MS, liquid chromatography-tandem mass spectrometry; MAP, mean arterial pressure; PTH, parathyroid hormone; SCOPE, Screening for Pregnancy Endpoints study; SGA, small-for-gestational-age

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Abstract (298 words)

Background: Associations of vitamin D with perinatal outcomes are inconsistent and few have considered the wider calcium metabolic system.

Objective: To explore functional vitamin D deficiency in pregnancy by investigating associations between vitamin D status, parathyroid hormone and perinatal outcomes.

Design: SCOPE (Screening for Pregnancy Endpoints) Ireland is a prospective cohort study of low risk, nulliparous pregnant women. We measured serum 25-hydroxyvitamin D [25(OH)D] and parathyroid hormone [PTH] at 15 weeks' gestation in 1754 participants.

Results: Mean ± SD 25(OH)D was 56.6 ± 25.8 nmol/L (22.7 ± 10.3 ng/mL) and geometric mean (95% CI) PTH was 7.84 (7.7, 8.0) pg/mL [0.86 (0.85, 0.88) pmol/L]. PTH was elevated in 34.3% of women who had 25(OH)D <30 nmol/L and in 13.9% of those with 25(OH)D ≥75 nmol/L. While 17% had 25(OH)D <30 nmol/L, 5.5% had functional vitamin D deficiency, defined as 25(OH)D <30 nmol/L plus elevated PTH. Elevated mean arterial pressure (MAP), gestational hypertension, preeclampsia and small-for-gestational-age (SGA) birth were confirmed in 9.2%, 11.9%, 3.8% and 10.6% of participants, respectively. In fully adjusted regression models, neither low 25(OH)D nor elevated PTH alone increased risk of any individual outcome. The prevalence of elevated MAP (19.1% vs. 9.7%) and SGA (16.0% vs. 6.7%) were highest (P <0.05) in those with functional vitamin D deficiency compared to the reference [25(OH)D ≥75 nmol/L and normal PTH]. The adjusted prevalence ratio (PR) and relative risk (RR) (95% CIs) for elevated MAP and SGA were 1.83 (1.02, 3.27) and 1.53 (0.80, 2.93), respectively. There was no effect of functional vitamin D deficiency on the risk of gestational hypertension [adjusted RR (95% CI); 1.00 (0.60, 1.67)] or preeclampsia [adjusted RR (95% CI); 1.17 (0.32, 4.20)].

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Conclusions: The concept of functional vitamin D deficiency, reflecting calcium metabolic stress, should be considered in studies of vitamin D in pregnancy.

Key words: Vitamin D, 25-hydroxyvitamin D, parathyroid hormone, pregnancy, perinatal, mean arterial pressure, gestational hypertension, preeclampsia, small-for-gestational-age

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Introduction

Pregnancy represents a period of particular nutritional vulnerability for the mother and developing fetus and nutritional deficits can adversely affect perinatal outcomes. Low vitamin D status [assessed by blood levels of 25-hydroxyvitamin D (25(OH)D)] in pregnancy is prevalent worldwide, in Caucasian and other ethnicities (1-3). Although low 25(OH)D has been associated with adverse perinatal outcomes including preeclampsia and small-for gestational-age (SGA) birth (4, 5), there is inconsistency in the literature (6). Vitamin D classically functions as part of the calcium metabolic system which maintains serum calcium within a critical narrow physiological window (7). Despite this long recognised metabolic connection, vitamin D and calcium are most often considered in isolation in terms of perinatal outcomes, with a lack of consideration for interactive effects (8). Although attenuated, the inverse relationship between 25(OH)D and calciotropic parathyroid hormone (PTH) is maintained in pregnancy in spite of the many changes in vitamin D and calcium metabolism (9). Secondary hyperparathyroidism refers to elevation of PTH resulting from low 25(OH)D and/or low calcium intake (10) and represents functional vitamin D deficiency.

Scholl and colleagues described the concept of calcium metabolic stress in pregnancy, in which adverse effects of vitamin D deficiency are mediated through a functional impact on the calcium metabolic system (assessed by measurement of PTH) (11, 12). To the best of our knowledge, these associations have not been replicated in a large, well-characterized pregnancy cohort. We aimed to test the concept of calcium metabolic stress by exploring associations of 25(OH)D, PTH and functional vitamin D deficiency at 15 weeks' gestation with adverse perinatal outcomes, including elevated mean arterial pressure (MAP), gestational hypertension, preeclampsia and SGA birth in a large cohort of low risk pregnant women.

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Subjects and Methods

Study design and participants

The Screening for Pregnancy Endpoints (SCOPE) study (www.scopestudy.net), an international, multi-center, prospective cohort study was designed with the primary aim of developing screening tests to predict adverse pregnancy outcomes, with preeclampsia as the primary outcome variable (13). SCOPE Ireland recruited 1792 participants who were attending antenatal care at Cork University Maternity Hospital, Cork, Ireland (51.9°N) between March 2008 and February 2011. Full clinical and methodological study details have been published previously (13). In summary, nulliparous women were eligible for inclusion provided the pregnancy was a low risk singleton pregnancy at less than 16 weeks' gestation. Exclusion criteria included pregnancies at increased risk of preeclampsia, SGA or spontaneous preterm birth due to specific underlying medical conditions or medical history, known major fetal anomaly or abnormal karyotype and interventions that could modify the outcome of pregnancy, such as aspirin treatment.

Extensive data on family situation, lifestyle and demographics, including current smoking, alcohol and drug use, supplement use, activity, employment and medical history were collected by trained research midwives. As a pre-pregnancy measurement was not possible, and given the well-established systematic bias in self-report of weight and height, maternal height and weight at 15 weeks' gestation were measured for calculation of BMI (14). Two consecutive blood pressure (BP) measurements were taken using a mercury or aneroid sphygmomanometer and proteinuria was assessed by semi-quantitative automated dip-stick reading. All demographic, anthropometric and clinical data were entered into a secure internet deployed database (MedSciNet AB, Stockholm, Sweden). Non-fasting blood samples were collected, processed to serum and stored at -80°C within 4 hours of collection.

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SCOPE was conducted in accordance with the Declaration of Helsinki guidelines and ethical approval was obtained from the Clinical Research Ethics Committee of the Cork Teaching Hospitals [ECM5(10)05/02/2008]. SCOPE is registered at the Australian, New Zealand Clinical Trials Registry (http://www.anzctr.org.au), ID: ACTRN12607000551493. Written informed consent was provided by all participants at commencement of the study, which was on average, at 15 weeks of gestation.

Clinical definition of outcomes

Perinatal outcomes were precise and predefined (13), with participants followed prospectively throughout pregnancy and delivery. MAP was calculated from systolic and diastolic BP measurements as diastolic BP + [(systolic BP – diastolic BP)/3], with MAP > 90 mmHg denoting elevated MAP. Gestational hypertension was defined as a systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg on at least two occasions four hours apart after 20 weeks' of gestation but before the onset of labor. Preeclampsia was gestational hypertension with either proteinuria (24 hour urinary protein ≥ 300 mg or spot urine protein:creatinine ratio ≥ 30 mg/mmol creatinine or urine dipstick protein ≥ 2+) or any multi-system complication of preeclampsia. SGA birth was defined as a birth weight < 10^{th} customized centile adjusted for maternal height, booking weight and ethnicity as well as gestation at delivery and infant sex (15).

Biochemical Analysis

Serum 25(OH)D

Measurement of 25(OH)D in our laboratory has been detailed previously (16). Briefly, total 25(OH)D was calculated by summation of individually quantified 25(OH)D_2 and 25(OH)D_3. Serum 25(OH)D_2 and 25(OH)D_3 concentrations were measured in using liquid chromatography-tandem mass spectrometry (LC-MS/MS) on a Waters Acquity UPLC

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system coupled to an Acquity Triple Quadrupole (TQD)® mass spectrometer detector (Waters, Milford, USA). Four levels of serum-based NIST (National Institute of Standards and Technology) certified quality assurance material (SRM 972) were used for method validation while quality control materials assayed in parallel to all samples were purchased from Chromsystems (Munich, Germany). NIST calibrators (SRM 2972) were used throughout the analysis. The limit of detection (LoD) for $25(OH)D_3$ and $25(OH)D_2$ was 0.31 and 0.44 nmol/L, respectively. The limit of quantitation (LoQ) for $25(OH)D_3$ and $25(OH)D_2$ was 1.03 and 1.43 nmol/L, respectively. Intra- and inter- assay CVs for both metabolites were < 6% and < 5% respectively. The laboratory of the Cork Centre for Vitamin D and Nutrition Research is accredited by the CDC Vitamin D Standardization Certification program and participates in the Vitamin D External Quality Assessment Scheme (DEQAS) (Charring Cross Hospital, London, UK).

Serum PTH

Serum intact PTH was measured using an ELISA (MD Biosciences Inc., Minnesota, USA) on the automated Dynex DS2® ELISA processing platform (Dynex Technologies, Virginia, USA). This two-site assay is designed to measure biologically intact PTH 1-84 and utilizes two purified goat polyclonal antibodies, each specific to a distinct region on the PTH molecule. A biotinylated antibody binds to mid-region and C-terminal PTH 39-84. The detection antibody, a horseradish peroxidase conjugated antibody, binds N-terminal PTH 1-34. PTH was measured in duplicate in 1497 participants and in singular in a further 257 participants as serum volume was insufficient for duplicate measurement. Geometric mean PTH concentration did not differ between duplicate and single measurements (independent samples t-test, $P = 0.10$) and single and duplicate measurements were collated for analysis, giving a total of 1754 PTH measurements. Intra- and inter- assay CVs for intact PTH were < 5% and < 7% respectively.

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Statistical analysis

Statistical analysis was performed using IBM SPSS® version 22.0 (IBM Corp., Armonk, NY, USA) and SAS® version 9.4 (SAS Institute Inc., Cary, NC, USA) software for Windows™. A full dataset, with no missing information, was available for all participants (*n* = 1754) and analysis was carried out without imputation. PTH was natural log-transformed to an approximately normal distribution and log PTH was used in analysis. Descriptive statistics were prepared for participants and independent samples t-test or ANOVA were used as appropriate to assess differences in mean concentrations of 25(OH)D and PTH within maternal characteristics. Post-hoc comparisons used Bonferroni correction. 25(OH)D is reported as mean ± SD and PTH as geometric mean (95% CI). The 25(OH)D/PTH relationship was graphically depicted by a scatter plot with Lowess curve (locally weighted regression smoothing scatterplot). ANOVA with Bonferroni corrected post-hoc analysis was performed to assess PTH concentrations across categories of 25(OH)D. Occurrence of adverse outcomes was compared between 25(OH)D/PTH categories using Chi-square tests (or Fisher's test as appropriate).

Associations between predictors and outcomes were assessed by log-Poisson regression, with regression models constructed to examine the effects of low 25(OH)D and elevated PTH, both individually and in combination, on adverse outcomes. While the full distribution of 25(OH)D was explored, and 25(OH)D and PTH were described across the range of 25(OH)D values, we considered low vitamin D status as 25(OH)D < 30 nmol/L (7) and replete status ≥ 75 nmol/L (17). These categories were used in regression models to allow simple comparison between groups of interest i.e. those with a low and replete vitamin D status. In the absence of pregnancy-specific reference ranges, we defined elevated PTH as greater than the 80th percentile. However, to minimize potential influence of undiagnosed pathological conditions relating to PTH, we excluded the top 2.5% of PTH concentrations. Thus, participants with

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PTH between the 80th and 97.5th percentiles were classed as having elevated PTH. Reference groups were 25(OH)D ≥ 75 nmol/L and normal PTH (i.e. PTH ≤ 80th percentile). Non-white participants (n = 40) were excluded from regression models.

Separate log-Poisson regression models (12 in total) were built for each predictor-outcome association based on both statistical goodness of fit of the model and clinical and theoretical knowledge. To circumvent the problem of large standard errors obtained with standard Poisson regression, we used Zou's modified Poisson approach which leads to the estimation of robust error variance and produces correct confidence intervals (18). To obtain best fit models the following steps were taken. Univariable analysis was used to assess the association between each potential covariate and the outcome of interest, with inclusion based on significance at alpha = 0.25. A multivariable model including all significant covariates from the univariate analysis was constructed. The association of interaction terms with each outcome was examined, and interaction terms were included in multivariable models if significant (at alpha = 0.10) and clinically meaningful. To support the statistical model building process clinical and theoretical knowledge of established associations between variables along with directed acyclic graphs (DAGs) were used to develop a theoretical framework of covariate-predictor-outcome relationships and to determine the role of each covariate (e.g. confounder, intermediate, collider) in the model, aiding in decision making during model development. This process resulted in an individual best-fit log-Poisson regression model for each of the 12 predictor-outcome models. Although all associations were examined using the same modified log-Poisson approach detailed above, because 25(OH)D, PTH and MAP were measured at the same time point associations are presented as prevalence ratios (PR) and 95% CIs while associations of 25(OH)D and PTH with gestational hypertension, preeclampsia and SGA are expressed as relative risks (RR) and 95% CIs.

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Results

Descriptive results

Participant characteristics and 25(OH)D and PTH concentrations in the SCOPE Ireland pregnancy cohort (n = 1754) are shown in **Table 1**. Mean ± SD 25(OH)D concentration was 56.62 ± 25.8 nmol/L (22.7 ± 10.3 ng/mL) and geometric mean (95% CI) PTH was 7.84 (7.7, 8.0) pg/mL [0.86 (0.85, 0.88) pmol/L]. This predominantly white (97.7%) cohort had a mean ± SD age of 30.5 ± 4.5 years and BMI of 24.9 ± 4.2 kg/m^2. At 15 weeks of gestation, 10.0% and 16.4% of participants, respectively, reported current smoking and alcohol consumption. Multi-nutrient supplements were consumed by 40% of participants and this was associated with significantly higher 25(OH)D and lower PTH concentrations in consumers ($P < 0.001$ for both). White ethnicity was also associated with higher 25(OH)D and lower PTH than other ethnicities ($P \leq 0.001$ for both). Although season of entry was significantly associated with 25(OH)D concentration ($P < 0.001$), PTH did not change with season. PTH increased and 25(OH)D decreased with increasing BMI category at 15 weeks of gestation; however post-hoc analysis revealed a significant decrease in 25(OH)D only in obese participants (BMI ≥ 30 kg/m^2) compared to those with a normal BMI. PTH concentration was highest in the small proportion of participants (1.2%) with a BMI < 18.5 kg/m^2. Mean arterial pressure was 79.1 ± 7.6 mmHg and 9.2% of participants had elevated MAP (> 90 mmHg). The prevalence of gestational hypertension, preeclampsia and SGA in the cohort were 11.9%, 3.8% and 10.6%, respectively.

Associations of 25(OH)D, PTH and functional vitamin D deficiency with perinatal outcomes

The lowess curve in **Figure 1** illustrates a decrease in PTH across a broad range of increasing 25(OH)D concentrations, with a decline in rate of decrease evident between 40 - 50 nmol/L. **Table 2** depicts PTH concentrations across the distribution of 25(OH)D, showing that PTH

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decreased significantly with increasing 25(OH)D ($P < 0.001$). Elevated PTH occurred more commonly ($P < 0.05$) in participants with 25(OH)D < 30 nmol/L (34.3%) than those ≥ 75 nmol/L (13.9%). In terms of vitamin D status, 44% of women had 25(OH)D < 50 nmol/L and 17% were below 30 nmol/L, while 25% were had 25(OH)D ≥ 75 nmol/L. In the stratified analysis of 25(OH)D and PTH, the prevalence of functional vitamin D deficiency, defined as 25(OH)D < 30 nmol/l plus PTH > 80th percentile, was much lower, at 5.5%, with 11.4% having a 25(OH)D < 50 nmol/L plus PTH > 80th percentile.

Associations of 25(OH)D, PTH and 25(OH)D/PTH groupings with elevated MAP are shown in **Table 3**. The prevalence of elevated MAP was not significantly higher (12.0% versus 9.3%) in participants with 25(OH)D < 30 nmol/L compared with 25(OH)D ≥ 75 nmol/L ($P > 0.05$). While there was an association of elevated PTH with elevated MAP [PR (95% CI); 1.49 (1.08, 2.04)], this trend was attenuated with covariate adjustment. Stratification of participants by 25(OH)D/PTH, shown in Table 3, revealed a prevalence of elevated MAP of 19.1% in those with functional vitamin D deficiency compared with 9.7% in the reference group [25(OH)D ≥ 75 nmol/L and normal PTH] ($P < 0.05$), translating to an adjusted PR (95% CI) of 1.83 (1.02, 3.27). Prevalence of elevated MAP did not increase with 25(OH)D < 30 nmol/L if PTH was not elevated [adjusted PR (95% CI); 0.91 (0.50, 1.65)].

Table 4 shows the associations of 25(OH)D, PTH and 25(OH)D/PTH groupings with gestational hypertension, preeclampsia and SGA birth. Having a 25(OH)D < 30 nmol/L increased the risk of SGA in crude but not adjusted analysis. There was no association of elevated PTH with gestational hypertension, preeclampsia or SGA. In combined 25(OH)D/PTH groupings, the prevalence of gestational hypertension was highest with elevated PTH and did not vary with 25(OH)D (both 18%, $P > 0.05$). Having functional vitamin D deficiency did not increase risk of gestational hypertension compared to the

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reference, which was 25(OH)D ≥ 75 nmol/L with normal PTH [adjusted RR (95% CI); 1.00 (0.60, 1.67)].

The lowest prevalence of preeclampsia (1.9%) was in those with 25(OH)D ≥ 75 nmol/L and normal PTH, compared to 5.0% when 25(OH)D ≥ 75 nmol/L with elevated PTH ($P > 0.05$). In those with 25(OH)D < 30 nmol/L, the prevalence of preeclampsia did not differ depending on PTH status ($P > 0.05$). Occurrence of preeclampsia was not significantly increased (4.3% versus 1.9%) with functional vitamin D deficiency compared to the reference group ($P > 0.05$) [adjusted RR (95% CI); 1.17 (0.32, 4.20)].

The proportion of participants with a SGA newborn in the reference group (6.7%) was lower than any other group, while 16% of those with functional vitamin D deficiency had a SGA birth ($P < 0.05$). A 2-fold increase in risk [RR (95% CI); 2.38 (1.31, 4.33)] was attenuated [adjusted RR (95% CI); 1.53 (0.80, 2.93)] in a fully adjusted model including BMI, smoking, university education, job status, recreational walking and multi-nutrient supplementation. A 25(OH)D concentration ≥ 30 - < 75 nmol/L with elevated PTH was not associated with SGA or any other outcome (data not shown). Regression models were repeated for all outcomes using a 25(OH)D cut-off of < 50 nmol/L; no associations were observed in multivariate models (data not shown).

Discussion

Inconsistencies in associations of maternal vitamin D status and perinatal outcomes are multifactorial (4, 5, 19) but it is likely that calcium-vitamin D interactions, largely ignored, could be a critical consideration (8, 11, 12). In this largest study to date of 25(OH)D, PTH and pregnancy outcomes, we report a two-fold increased prevalence ratio of elevated MAP in women with functional vitamin D deficiency, defined by 25(OH)D < 30 nmol/L and elevated

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PTH, versus those with 25(OH)D ≥ 75 nmol/L and normal PTH. This increase was present with low vitamin D status only if PTH was concurrently elevated. A similar trend was observed for SGA, although this was attenuated in regression models. Functional vitamin D deficiency did not increase risks of gestational hypertension or preeclampsia, although prevalence of preeclampsia was lowest, at 1.9%, in the reference group.

Our analysis follows earlier analyses by Scholl et al (11, 12), who reported that women with functional vitamin D deficiency and calcium metabolic stress were two-three-fold more likely to develop preeclampsia and SGA. Mixed parity women recruited to their multi-ethnic (86% black or Hispanic) study were generally young (69% < 25 years of age) and of low socioeconomic status (11, 12). We aimed to extend the concept of functional vitamin D deficiency to a prospective cohort of well-characterized women in Northern Europe. Participants in the SCOPE Ireland cohort were nulliparous with low risk pregnancies, generally well-educated, mostly white and 89% were ≥ 25 years of age. In this cohort, as in the literature (20), clear differences in both 25(OH)D and PTH were evident between white and other ethnicities, highlighting the need for explorations of vitamin D and the calcium metabolic system that are specified by ethnicity. Thus, we restricted our current analysis to white participants as the numbers of other ethnic groups were too small to analyze separately.

The prevalence of low vitamin D status in our cohort was higher than in many cohorts at similar latitude, reflective of the lack of a mandated maternal supplementation policy, analytical sensitivity and accuracy as well as inclement prevailing weather (16). Given that we previously observed a reduction in the combined prevalence of preeclampsia+SGA with 25(OH)D ≥ 75 nmol/L (16) we chose this as the reference value for 25(OH)D and defined low 25(OH)D status as < 30 nmol/L (7). There is a lack of clarity with regard to PTH threshold levels in pregnancy, as PTH decreases in early gestation (21), reducing the applicability of non-pregnancy thresholds. In this context, and given the population specific

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nature of PTH (22), as well as well-documented, substantial analytical differences between methods (23-27), we used a percentile cut-off, which although crude, may best capture elevated PTH at a sample specific level. Additionally, we excluded the top 2.5% of PTH values to minimise the risk of including undiagnosed cases of primary hyperparathyroidism, which may have produced artificially elevated outcome risks. Although sample specific, there may be some potential for misclassification of participants with use of a percentile cut-off as a result of inherent inter-individual variation in PTH. Concentrations of PTH were lower in our cohort than other studies (9, 11, 28, 29), but direct comparison is difficult; analytical method, gestation and ethnicity influence PTH, as do specimen type (30) and BMI (31).

High PTH has been associated with blood pressure (32, 33) and cardiovascular risk indicators (34), and there are a number of biologically plausible mechanisms through which the calcium metabolic system may impact blood pressure. Belizán et al proposed that high PTH increases intracellular calcium, triggering contraction of vascular smooth muscle cells and vasoconstriction (35). Evidence of inter-play between the calcium metabolic system and renin-angiotensin-aldosterone system is accumulating (36). Hemodynamics can be explored through a range of measures and because a meta-analysis (n = 60,599) reported a second trimester MAP > 90 mmHg to be predictive of preeclampsia (37) we investigated this outcome in addition to gestational hypertension and preeclampsia. Although we report that those with functional vitamin D deficiency were two-fold more likely to have elevated MAP at 15 weeks' gestation, there was no increase in risk of gestational hypertension. Given that 25(OH)D, PTH and MAP were all measured at 15 weeks' gestation, this may reflect a time-point specific occurrence. Elevated MAP and gestational hypertension are not mutually inclusive outcomes; in this cohort 36% of those with elevated MAP at 15 weeks' developed gestational hypertension and these outcomes may reflect different health profiles. Gestational

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hypertension can occur at any stage in the second half of pregnancy and requires close monitoring and treatment as clinically indicated (38).

Considering preeclampsia, the effect of vitamin D supplementation is not clear (19, 39). However, combined vitamin D and calcium supplementation significantly reduced risk of preeclampsia in three trials of 1,114 women (19). None of these trials compared each nutrient individually versus combined supplementation and placebo. In a cohort in which 6% developed preeclampsia, Scholl et al reported that participants with functional vitamin D deficiency at < 20 weeks' gestation were three times more likely to develop preeclampsia (11). Despite a substantially larger sample size, we did not replicate this effect, potentially due to analytical differences and our application of a refined estimate of elevated PTH in a 'trimmed' distribution. The inclusion criteria for SCOPE, focusing on women with low risk pregnancies, likely resulted in a different disease profile in those who developed preeclampsia between the two cohorts; a relevant consideration given potential differences in beneficial effects of vitamin D and calcium dependent on disease type and risk profile (40, 41). However, the lowest prevalence of preeclampsia occurred in those with 25(OH)D ≥ 75 nmol/L with normal PTH, indicating a potential benefit of higher serum 25(OH)D, as suggested by Aghajafari et al (4), particularly if PTH is not elevated.

With regards to SGA, fetal skeletal development represents a potential mechanism through which perturbations in the maternal calcium metabolic system could predispose to SGA (42, 43) and interactions between vitamin D and calcium on fetal bone growth have been noted in pregnant adolescents (44), a unique group due to dual growth requirements. Elevated blood pressure can also predispose to SGA birth, both in association with and independently of preeclampsia (45-47). Causative effects of vitamin D and calcium on fetal growth and SGA have not been definitively established (39, 41, 48, 49). Observational evidence suggests associations of both dairy intakes and PTH with fetal growth (50-52). A secondary analysis

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of trial data in Gambian women, found no synergistic effect of calcium supplementation and 25(OH)D on fetal growth (53). There was little evidence of vitamin D deficiency in the Gambian population who had low habitual calcium intakes, and these data may not be applicable in our setting with prevalent vitamin D deficiency. In our analysis we did not distinguish between SGA neonates born constitutionally small and those with fetal growth restriction resulting in SGA, in whom outcomes may be worse (54).

To our knowledge, this is the largest study to investigate vitamin D and PTH in the context of pregnancy and perinatal outcomes. Our data are strengthened by use of clinically defined outcomes and the gold standard technique of CDC-accredited LC-MS/MS for measurement of 25(OH)D. However, we did not have access to calcium intake data; this would have enabled a more specific examination of calcium metabolic stress and perinatal outcomes, although inclusion of PTH may capture some variation resulting from differences in calcium intake. Harmonization and standardization of PTH analysis is required to define reference ranges for pregnancy and for the purposes of this field, to better describe the 25(OH)D/PTH relationship during gestation. In the absence of these data, the clinical significance of elevated PTH is difficult to interpret.

In summary, prevalence of SGA was highest with functional vitamin D deficiency and we have demonstrated evidence of functional vitamin D deficiency and elevated MAP, reflecting the adverse impact of stress to the maternal calcium metabolic system in women at 15 weeks of gestation. Though challenging in design and resource allocation, consideration should be given to a priori inclusion of calcium intakes as well as quality-assured 25(OH)D and PTH measurement in future studies of vitamin D and perinatal health.

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Table 1

Sample characteristics, PTH and 25(OH)D concentrations in the SCOPE Ireland pregnancy cohort (n = 1754)[1]

Characteristic	%	25(OH)D		PTH	
		Concentration (nmol/L)	*P*	Concentration (pg/mL)	*P*
All participants		56.62 ± 25.8	-	7.84 (7.7, 8.0)	-
Ethnicity			< 0.001		0.001
White	97.7	57.11 ± 25.8		7.79 (7.6, 8.0)	
Other	2.3	35.54 ± 19.9		10.28 (8.5, 12.5)	
Age (years)			< 0.001		0.15
< 25	11.5	49.38 ± 27.8		7.66 (7.1, 8.2)	
≥ 25 - < 30	30.3	58.47 ± 26.5[2]		7.91 (7.6, 8.3)	
≥ 30 - < 35	45.0	57.88 ± 24.8[2]		7.69 (7.4, 8.0)	
≥ 35	13.2	54.33 ± 24.8		8.38 (7.8, 9.0)	
BMI (kg/m^2)[3]			0.017		0.005[4]
< 18.5	1.2	54.39 ± 29.0		9.77 (7.1, 13.5)	
≥ 18.5 - < 25	58.4	58.14 ± 26.3		7.58 (7.4, 7.8)	
≥ 25 - < 30	28.1	55.30 ± 25.2		8.14 (7.8, 8.5)	
≥ 30	12.3	52.62 ± 24.3[5]		8.28 (7.7, 8.9)	
Smoking status[3]			< 0.001		0.08
No	90.0	57.66 ± 25.8		7.90 (7.7, 8.1)	
Yes	10.0	47.23 ± 24.4		7.34 (6.8, 7.9)	
Alcohol consumption[3]			0.10		0.47
No	83.6	56.17 ± 25.9		7.81 (7.6, 8.0)	
Yes	16.4	58.91 ± 25.5		8.00 (7.6, 8.5)	
Multi-nutrient supplementation[3]			< 0.001		< 0.001
No	60.1	48.70 ± 23.8		8.15 (7.9, 8.4)	
Yes	39.9	68.54 ± 24.2		7.40 (7.1, 7.7)	
Season of entry[6]			< 0.001		0.16

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Winter	58.4	49.54 ± 24.6		7.96 (7.7, 8.2)	
Summer	41.6	66.57 ± 24.2		7.68 (7.4, 8.0)	
Elevated MAP[3]			0.42		0.10
No	90.8	57.28 ± 25.6		7.73 (7.5, 7.9)	
Yes	9.2	55.61 ± 27.2		8.35 (7.6, 9.1)	
Gestational Hypertension			0.85		0.62
No	88.1	56.57 ± 25.8		7.82 (7.6, 8.0)	
Yes	11.9	56.93 ± 26.1		7.99 (7.4, 8.7)	
Preeclampsia			0.18		0.28
No	96.2	57.27 ± 25.8		7.77 (7.6, 8.0)	
Yes	3.8	52.97 ± 23.8		8.34 (7.3, 9.5)	
Small-for-gestational-age			0.003		0.16
No	89.4	57.74 ± 26.0		7.75 (7.5, 7.9)	
Yes	10.6	51.85 ± 23.3		8.20 (7.6, 8.9)	

[1]PTH, geometric mean (95% CI) (all such values); 25(OH)D, mean ± SD (all such values). Differences assessed using independent samples t-test for binary variables and ANOVA for variables with multiple categories. Post-hoc analysis used Bonferroni correction. PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D; SCOPE, Screening for Pregnancy Endpoints; MAP, mean arterial pressure.

[2]$P < 0.05$ compared to lowest group.

[3]At 15 week visit.

[4]Overall ANOVA significant but no significant between group differences after Bonferroni correction.

[4]$P < 0.05$ compared to BMI ≥ 18.5 - < 25 kg/m^2.

[6]Winter: November through May and Summer: June through October.

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Table 2

PTH concentration by 25(OH)D category in the SCOPE Ireland pregnancy cohort (n = 1754)[1]

25(OH)D (nmol/L)	%	PTH (pg/mL)
< 30	17.3	9.80 (9.2, 10.4)[3,4]
≥ 30 - < 40	13.6	8.50 (8.0, 9.1)[2,3,4]
≥ 40 - < 50	13.2	7.80 (7.3, 8.4)[2,4]
≥ 50 - < 75	30.7	7.54 (7.2, 7.9)[2,4]
≥ 75	25.2	6.78 (6.5, 7.1)[2,3]

[1]PTH geometric mean (95% CI) (all such values). Differences assessed using ANOVA. Overall *P*-trend for ANOVA, P < 0.001. Post hoc analysis used Bonferroni correction. PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D; SCOPE, Screening for Pregnancy Endpoints.

[2]*P* < 0.05 compared with < 30 nmol/L.

[3]*P* < 0.05 compared with 50 - 75 nmol/L.

[4]*P* < 0.05 compared with ≥ 75 nmol/L.

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Table 3

Association of 25(OH)D and PTH with elevated MAP in white participants of the SCOPE Ireland pregnancy cohort[1]

			Elevated MAP (> 90 mmHg)		
25(OH)D (nmol/L)	PTH (percentile)	n	%	Unadjusted	Adjusted
≥ 75	—	441	9.3	Reference	Reference
< 30	—	283	12.0	1.29 (0.84, 1.99)	1.46 (0.90, 2.38)[2]
—	≤ 80th	1338	9.3	Reference	Reference
—	> 80th	334	13.8	1.49 (1.08, 2.04)	1.28 (0.94, 1.75)[3]
≥ 75	≤ 80th	373	9.7	Reference	Reference
≥ 75	> 80th	60	8.3	0.86 (0.35, 2.11)	0.89 (0.34, 2.28)[4]
< 30	≤ 80th	180	8.3	0.86 (0.49, 1.53)	0.91 (0.50, 1.65)[4]
< 30	> 80th	94	19.1	1.98 (1.18, 3.33)	1.83 (1.02, 3.27)[4]

[1]Values are PRs (95% CIs). Log-Poisson regression was used to examine the association between 25(OH)D and PTH thresholds (individually and in combination) and risk of elevated MAP. 25(OH)D, 25-hydroxyvitamin D; PTH, parathyroid hormone; MAP, mean arterial pressure; SCOPE, Screening for Pregnancy Endpoints.

[2]25(OH)D-MAP model adjusted for BMI, maternal age, university education and supplementation.

[3]PTH-MAP model adjusted for BMI, maternal age, smoking, supplementation, recreational walking and alcohol consumption.

[4]25(OH)D/PTH-MAP model adjusted for BMI, maternal age, smoking, supplementation and recreational walking.

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Table 4

Associations of 25(OH)D and PTH with gestational hypertension, preeclampsia and SGA in white participants of the SCOPE Ireland pregnancy cohort[1]

			Gestational Hypertension			Preeclampsia			Small-for-gestational-age		
25(OH)D (nmol/L)	PTH (percentile)	n	%	Unadjusted	Adjusted	%	Unadjusted	Adjusted	%	Unadjusted	Adjusted
≥ 75	—	441	14.3	Reference	Reference	2.3	Reference	Reference	7.3	Reference	Reference
< 30	—	283	12.7	0.89 (0.61, 1.30)	0.76 (0.51, 1.13)[2]	4.9	2.18 (0.98, 4.84)	1.06 (0.42, 2.68)[3]	13.1	1.80 (1.15, 2.82)	1.18 (0.70, 1.99)[4]
—	≤ 80th	1338	11.3	Reference	Reference	3.7	Reference	Reference	10.3	Reference	Reference
—	> 80th	334	14.7	1.30 (0.96, 1.75)	1.18 (0.87, 1.59)[5]	4.5	1.20 (0.68, 2.11)	1.13 (0.63, 2.00)[6]	10.8	1.05 (0.74, 1.48)	1.00 (0.71, 1.43)[7]
≥ 75	≤ 80th	373	13.7	Reference	Reference	1.9	Reference	Reference	6.7	Reference	Reference
≥ 75	> 80th	60	18.3	1.34 (0.74, 2.42)	1.24 (0.62, 2.50)[8]	5.0	2.66 (0.71, 10.02)	2.36 (0.68, 8.22)[9]	11.7	1.74 (0.79, 3.85)	1.72 (0.77, 3.88)[10]
< 30	≤ 80th	180	10.0	0.73 (0.44, 1.21)	0.61 (0.37, 1.02)[8]	5.0	2.66 (1.01, 7.04)	1.32 (0.45, 3.87)[9]	10.6	1.57 (0.89, 2.78)	0.97 (0.52, 1.81)[10]
< 30	> 80th	94	18.1	1.32 (0.80, 2.18)	1.00 (0.60, 1.67)[8]	4.3	2.27 (0.68, 7.58)	1.17 (0.32, 4.20)[9]	16.0	2.38 (1.31, 4.33)	1.53 (0.80, 2.93)[10]

[1]Values are RRs (95% CIs). Log-Poisson regression was used to examine the association between 25(OH)D and PTH (individually and in combination) and risk of gestational hypertension, preeclampsia and SGA. 25(OH)D, 25-hydroxyvitamin D; PTH, parathyroid hormone; SGA, small-for-gestational-age; SCOPE, Screening for Pregnancy Endpoints.

[2]25(OH)D-gestational hypertension model adjusted for BMI, smoking and recreational walking.

[3]25(OH)D-preeclampsia model adjusted for BMI, university education, and supplementation.

[4]25(OH)D-SGA model adjusted for university education, job status, supplementation and recreational walking.

[5]PTH-gestational hypertension model adjusted for BMI, smoking, supplementation, moderate exercise and infant sex.

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[6]PTH-preeclampsia adjusted for BMI, university education, supplementation, moderate exercise and infant sex.

[7]PTH-SGA model adjusted for BMI, university education, job status, smoking and moderate exercise.

[8]25(OH)D/PTH-gestational hypertension model adjusted for BMI and recreational walking.

[9]25(OH)D/PTH-preeclampsia model adjusted for BMI, university education and supplementation.

[10]25(OH)D/PTH-SGA model adjusted for BMI, smoking, university education, job status, supplementation and recreational walking.

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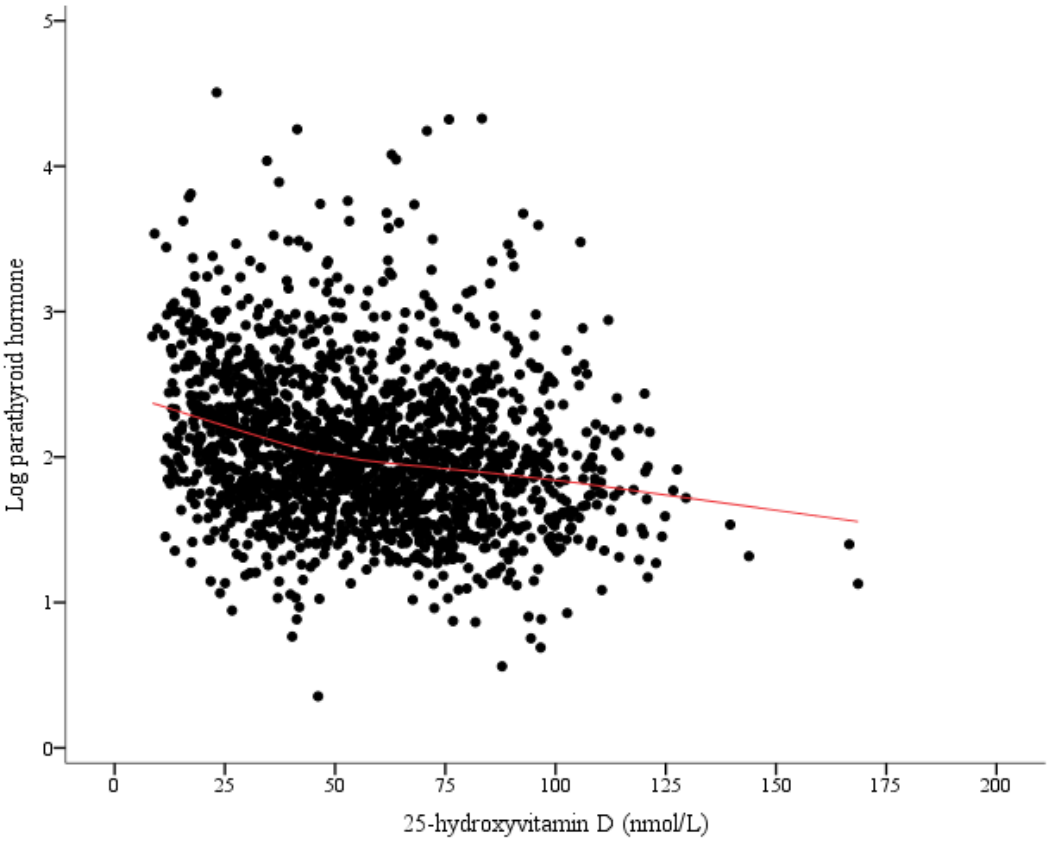

Figure 1. Scatterplot with Lowess curve of log parathyroid hormone and 25-hydroxyvitamin D in participants of the SCOPE Ireland pregnancy cohort (*n* = 1754).