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The effect of maternal vitamin D status on pregnancy outcome and child health in the first year of life

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Summary

Aim: To study the relationship of maternal vitamin D level at the moment of delivery with gestational and infant outcomes. *Materials and Methods:* A single centre prospective cohort study. Main outcomes were birth weight percentile and respiratory tract infections in the first year, secondary outcomes gestational diabetes, preterm birth, pre-eclampsia, caesarean birth, and atopic dermatitis and gastroenteritis in the first year of life. Maternal vitamin D was determined in venous plasma after delivery, infant data were prospectively gathered through a diary kept by the parents. *Results:* A total of 240 deliveries was included. Vitamin D insufficiency was present in the large majority (n=205, 95.5%) In univariate analysis a significant association was found between vitamin D level < 10 ng/ml and birthweight < P10, but in multivariate analysis including parity, maternal age, fetal sex, gestational diabetes, maternal glucose level, and preeclampsia there was no significant contribution from low vitamin D. For only 37 (15%) infants complete follow up data for one year were available. An association was found between lower vitamin D and more than two respiratory tract infections; this relations disappeared when taking into account birthweight, breastfeeding, and having a sibling going to daycare. No relation was present between vitamin D and pre-eclampsia, caesarean birth, atopic dermatitis, and gastroenteritis. *Conclusions:* The actual cut off values for vitamin D should be questioned as over 90% of the population would be deficient. When considering other factors, maternal vitamin D at the moment of delivery does not correlate with birthweight percentile, respiratory tract infections in the first year of life, nor other frequent obstetric and infant problems.

Key words: Vitamin D; Pregnancy; Preeclampsia; Gestational diabetes; Birthweight; Child health; Respiratory tract infection.

Introduction

Vitamin D (25(OH)D) can be synthesised in the skin through exposure to UV-light or can be obtained through dietary intake [1]. The effect of vitamin D on calcium metabolism and bone health has long been known. Since the discovery of rickets [2], more recently effects on muscle function, the nervous, cardiovascular, and immune system have been intensively studied [1, 3-5]. A strong association exists between maternal and fetal 25(OH)D status[6] and maternal vitamin D deficiency may have deleterious effects on gestational and neonatal outcomes. A relation between maternal vitamin D and the prevalence of bacterial vaginosis [7], gestational diabetes [8], pre-eclampsia [9, 10], preterm birth[11], caesarean section [12, 13], and small for gestational age (SGA) [14] has been described. Children whose mother has suffered from vitamin D deficiency during pregnancy may also be more likely to have a lower birthweight [14], lower femur volume [15], and more infections and atopic dermatitis [16, 17]. Even long-term effects on cardiovascular disease, autoimmune diseases, and cancers have been suggested [18].

Vitamin D deficiency is by consensus defined as a 25(OH)D ≤ 20 ng/ml and vitamin D insufficiency as a 25(OH)D of 21-29 ng/ml [19]. However, serum vitamin D level in the population generally shows a normal distribution, the mean minus two standard deviations often noted at around 10 ng/ml. Recent studies suggest that these cut-off values may not be adequate, which could either mean that higher vitamin D levels need to be pursued, or that cut-off values need to be lowered [4, 5, 9, 18, 20-22].

Vitamin D deficiency is very common and the incidence highly depends on the definition used. It is generally more common in non-Western ethnic groups. These differences may be caused by differences in skin type, skin covering, and the avoidance of direct sun exposure [23].

Even less is known about effects and side effects of vitamin D supplementation in pregnancy. No clear benefits of supplementation have been demonstrated and precaution is needed when supplementing high doses of fat-soluble vitamins [4, 12, 17, 24-26]. Adverse effects of vitamin D supplementation such as cardiovascular disorders, hypercalcaemia, renal calculi, renal insufficiency, and gastrointestinal disorders have been reported [25, 27]. Therefore the present authors found it useful to study the effect of maternal vitamin D status on pregnancy outcome (e.g. gestational diabetes, birthweight, preterm birth, preeclampsia, and caesarian section) and child health in the first year of life, using a study population representative for this local

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mixed multiethnic society.

The aim of this study was to determine the relation of maternal vitamin D with both gestational and infant outcome. In the first part of this study, the main objective was to determine the relation between maternal vitamin D at the moment of delivery and infant on birthweight. In addition to birthweight, the authors aimed to study the relation with gestational diabetes, preterm birth, preeclampsia. and caesarean section. In part two, the main objective was to study the relation of maternal vitamin D status and the prevalence of respiratory tract infections in the first year of life of the young child. In addition to respiratory tract infections, the authors wanted to study the prevalence of atopic dermatitis and gastroenteritis.

Materials and Methods

A single centre prospective cohort study at the Antwerp University Hospital was performed. The study has been approved by the Institutional Ethics Committee of Antwerp University Hospital under reference 13/51/526.

Women were recruited at the maternity ward of Antwerp University Hospital. All women provided written informed consent prior to enrolment. Multiple pregnancies and women who were transferred to Antwerp University Hospital because of obstetric complications were excluded from the study as were women with pre-existing diabetes. For part two, two more exclusion criteria were used, namely parents with insufficient knowledge of the Dutch language to fill in the diary and children who stayed in the neonatal care unit for longer than one day.

25(OH)D levels were determined two days postpartum in maternal serum using chemiluminescence (CLIA). In this department at day 2, a routine blood test is performed and women are discharged from the maternity ward one day later.

Mothers were personally recruited by one of the investigators during their stay at the maternity after delivery. For part one of the study the authors obtained information from the medical records, mainly using the pregnancy files. They looked for the presence of gestational hypertension or preeclampsia, caesarean section, gestational diabetes, and glucose challenge test-values and preterm birth. For this study gestational hypertension was defined as systolic blood pressure > 140 mmHg and/ or diastolic > 90 mmHg on at least two occasions at least two hours apart and appearing de novo after 20 weeks. Pre-eclampsia was hypertension and at least 2+ proteinuria on a dipstick. Glucose challenge was performed between 24 and 28 weeks with a 50-gram glucose orally in a non-fasting patient on a venous sample at one hour after ingestion. Gestational diabetes was diagnosed after 75-gram glucose orally in a fasting patient according to WHO criteria. To assess low birthweight, gestational age was taken into account using percentiles available for the region of Flanders, Belgium [26]. The authors empirically defined low birth weight (LBW) as below or equal to the tenth percentile and fetal growth restriction (FGR) as below or equal to the fifth percentile

For part two, the parents were asked to complete a questionnaire and to keep track of their child's health using a diary that was provided. The diaries were interpreted by the researchers to quantify the number of respiratory tract and gastro-intestinal infections and the prevalence of atopic dermatitis. Respiratory and gastrointestinal infections and atopic dermatitis were accepted as diagnosis when given as such by the parents; no control was done from medical files as these were generally not available to the authors. The parents were contacted on average five times in a one year period to retrieve data collected.

Descriptive statistics were used to describe the present sample including maternal age, parity, mean vitamin D, birthweight, gestational age, and the occurrence of pregnancy complications (e.g. caesarean section, preeclampsia, gestational diabetes, LBW, and FGR. Vitamin D was studied both as a continuous variable with range and 95% confidence intervals and as different degrees of deficiency as reported in the literature as < 10 ng/ml, < 20 ng/ml, and < 30 ng/ml. Mean vitamin D levels were compared between different pregnancy outcomes.

Dichotomous variables were compared using Chi-squared test, significance accepted at $p < 0.05$ and odds ratios with 95% confidence intervals. For continuous variables, normality was checked by Shapiro Wilk test and the groups were compared using Student's *t*-test (significance accepted at $p < 0.05$). Univariate correlations were tested with linear regression. Significant differences were further evaluated in multivariate logistics regression including in the model maternal age, parity, fetal sex, gestational age, glucose value after challenge, and presence of gestational diabetes.

For part two, associations between maternal vitamin D levels and respiratory tract infections, atopic dermatitis, and gastroenteritis of the child in the first year of life were investigated, using multinomial and binary logistic regressions. As a single period of respiratory tract infection is almost universally present in young infants, the children of the study population in part two were subdivided into two categories, namely less or more than two respiratory tract infections during the first year of life. All statistical analyses were performed using SPSS Statistic 23.0.0.0.

Results

Part one

A total of 249 patients were included in part one of the study. Characteristics of the study population are presented in Table 1. Of the 249 patients included, 25(OH)D levels were determined in 217 patients two days postpartum (87.2%). The mean 25(OH)D level was 14.40 ng/ml (range 4–45 ng/ml; 95%CI: 13.37–15.42 ng/ml); 89 women had a 25(OH)D level <10 ng/ml (41.0%), 168 women < 20 ng/ml (77.4%), and 205 women < 30 ng/ml (95.5%).

Of these patients, 67 patients had a caesarean section (26.9%), of which 41 were elective (61.2%), 14 patients had developed preeclampsia (5.6%), and 14 had developed gestational diabetes (5.6%). Eighteen patients delivered early (≤ 37 weeks gestation) (7.2%) and 46 babies were considered to suffer from LBW (≤ P10) (18.5%); 25 (10.4%) demonstrated FGR (≤ P5). Mean vitamin D levels were compared within different pregnancy outcomes (Table 2).

After exclusion of preterm deliveries (gestational age < 37 weeks), birthweight was found to be normally distributed ($p = 0.137$). Chi squared test was used to find associations between vitamin D levels at different cut-off levels (< 10, < 20, and < 30 ng/ml) and the presence of LBW. An association was found if maternal vitamin D levels were <10 ng/ml ($p = 0.044$). However, in a logistic regression model including maternal age, parity, fetal sex, glucose

Table 1. — *Characteristics and outcomes of the study group.*

	N	%			
Total	217				
Female	110	50.6			
Male	107	49.4			
Cesarean section	58	26.9			
Pre-eclampsia	14	6.4			
Gestational diabetes	14	6.4			
	N (Missing)	Mean	Minimum	Maximum	95% Confidence Interval
Age (years)	217	30.2	20	44	29.7-30.9
Gestational age (weeks)	217	38.8	25	42	38.6-39.0
Birth weight (grams)	217	3314	810	4900	3238-3390
Serum glucose after challenge (mg/dl)	151(66)	111.6	63.0	194.0	107.4-115.8
25 OH vitamin D (ng/ml)	217	14.4	4	45	13.3-15.4

Table 2. — *Vitamin D levels for different obstetric complications.*

	Mean vitamin D (ng/ml)	95% CI
Pre-eclampsia	13.75	6.30−21.20
No pre-eclampsia	14.42	13.38−15.46
Gestational diabetes	15.42	7.87−22.97
No gestational diabetes	14.34	13.32−15.35
Preterm birth	16.62	9.83−23.41
Term birth	14.25	13.24−15.27
Low birth weight (≤ P10)	12.32	8.82−15.81
Birth weight > P10	14.63	13.56−15.71
Fetal growth restriction (≤ P5)	11.83	9.56−14.11
Birth weight > P5	15.01	13.87−16.15
Caesarean section	14.86	12.68−17.04
Vaginal delivery	14.23	13.07−15.40

challenge test-values, presence of gestational diabetes, and/or gestational hypertension, this association was no longer statistically significant.

When testing associations with birthweight of term infants and vitamin D, gestational age, parity, sex, glucose challenge test-values, and the presence of preeclampsia and gestational diabetes, using a linear regression, only parity appeared to be a significant factor ($p = 0.001$). When performing the same analysis without exclusion of preterm babies, associations have been found for parity ($p = 0.000$) as well as gestational age ($p = 0.000$). Adjusted R^2 for the model was 0.287, suggesting that only 28.7% of the variation in birthweight is predicted by this model. Linear regression resulted in the following model (sig ANOVA = 0.000): birthweight (grams)= -2811.345 + 176.725 (parity) + 146.431 (gestational age).

To determine the effect of vitamin D on the odds of having one of the pregnancy complications described earlier, logistic regressions were performed but no significant correlations were present.

Part two

Of the 249 patients of part one, 162 (65.1%) accepted to take part in the follow up study. Finally 42 of 162 patients (26%) filled in the diary during the entire year; all others were lost to follow up despite frequent telephone calls. Two of the remaining patients were excluded due to congenital anomalies diagnosed after inclusion and necessitating more than one day neonatal hospitalisation. Of the 40 remaining children, maternal 25 (OH) vitamin D levels were known in 37. All children had at least one period of respiratory tract infection, 22 of 37 children had more than two respiratory tract infections in the first year of life (59.5%) with a median of three respiratory tract infections (range 0-8). Ten of 37 children suffered from gastroenteritis (27%) and five of 37 children had suffered from atopic dermatitis (13.5%).

When performing logistic regression for vitamin D and the occurrence of more than two respiratory tract infections (RTI) during the first year of life, a strong association was found ($p = 0.004$; B = -0,103; constant 3.928) resulting in the model: odds (> 2 RTI/year) = Exp (3.928-0.103*vitamin D (ng/ml)). With a vitamin D value of 10 ng/ml, odds on having more than two RTIs is 18.138; meaning 94.8% of children in the present study population will have more than two RTI's during the first year of life. Using the same equation for a vitamin D value of 20 ng/ml and 30 ng/ml, odds is 6.475 and 2.312 respectively, meaning 86,6% and 69,8% of children will have more than two RTI's.

With birthweight, breastfeeding, having siblings, and going to daycare taken into account as possible confounders, the association was still statistically significant ($p = 0.047$). No significant associations were found for gastroenteritis and atopic dermatitis.

Discussion

This study presents follow up data for the first year of life related to maternal Vitamin D levels at the moment of delivery in a single university maternity. The main gestational outcome was low birth weight defined as below or

equal to the fifth percentile in a regional growth chart. The fact that 10% scores below the fifth percentile may be due to the high risk character of the population reached by a tertiary care center, which must warn against generalisation of the results. In general association between maternal vitamin D levels and outcomes was low and not significant.

When comparing mean vitamin D levels within different pregnancy outcomes, a significant e difference could be observed with LBW especially when vitamin D levels were below 10 ng/ml. When confounders were taken into account using multivariate analysis, this association was no longer significant. This suggests that any possible role played by Vitamin D in LBW is by far overruled by such factors as maternal age, parity, maternal glucose levels with or without hypertension or pre-eclampsia. The association found between maternal vitamin D and having more than two RTI's was rather strong and warrants further investigation.

The present authors realize this study demonstrates several weaknesses. Given the fact that the study was conducted in a single tertiary hospital, results should not be extrapolated to the general population. Selection bias may have occurred, considering the difference between a patient population in a tertiary hospital and that in a general regional hospital. If the study would have been conducted over different centers, the study population would have been more representative for the entire Antwerp population. Because of this, the present study population is expected to be more prone to pregnancy complications. This may lead to either an over- or underestimation of the contribution of vitamin D status.

Given the small study population, precaution needs to be taken when interpreting the present study results, especially due to the limited number (37/249; 15%) for whom complete follow up data for one year are available.

For part one of this study, inclusion was limited due to requirements imposed by the institutional Ethics Committee of Antwerp University Hospital. Written consent had to be acquired by one of the researchers personally for every patient before entering the study. Due to limitations in time available, only 249 (of 810; 30.7%) potentially available patients have been included during the timeframe of this study.

For part two the authors noted a poor response rate and compliance. Of the 162 women who agreed to participate, only 42 managed to complete the diary, giving a response rate of 26%. In addition to this poor response rate, the data obtained from the diaries were written by the parents and not by a health practitioner. There was no strict definition of respiratory tract infections or gastroenteritis; it was accepted as given by the parents. Moreover, several parents reported that their child suffered from chronic rhinitis. This made it difficult to correctly objectify the number of infections. In addition, the severity and the duration of the infections were not taken into account. The number of infections could also be related to the child's contact with other children, which was difficult to objectify in this study design. It was not feasible to achieve medical files of the babies as these were followed in community care, lacking centralised medical files.

Since the study was conducted longitudinally, data collection was spread throughout the year. Therefore, selection bias due to seasonal differences in vitamin D status should be as low as possible.

The main conclusion arises from the overall low mean vitamin D status. Given that vitamin D deficiency is defined as a 25(OH)D below 20 ng/ml and vitamin D insufficiency as a 25(OH)D of 21-29 ng/ml [19], only 4.5% of this study population would be defined as vitamin D sufficient. Noting that 74.7% of this study population took prenatal vitamin D supplementation, one may ask if vitamin D is sufficiently present in prenatal vitamins or that cut-off values are placed too high. Nonetheless, an association between vitamin D levels and supplementation has been found, suggesting some response to vitamin D supplementation.

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