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Sub-optimal maternal vitamin D status and low education level as determinants of small for gestational age birth weight

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ABSTRACT

Objective

This study aimed firstly to investigate the contribution of maternal 25(OH) vitamin D to the association of maternal education and small for gestational age (SGA) and secondly to examine whether the contribution of 25(OH) vitamin D differs by overweight, season, and maternal smoking.

Methods

Logistic regression analysis using data of 2274 pregnant women of Dutch ethnicity from the ABCD study, a population-based cohort study in the Netherlands. Maternal 25(OH) vitamin D was measured in early pregnancy. Stratified analyses were done for overweight, season of blood sampling, and smoking.

Results

Low-educated women had lower 25(OH) vitamin D levels compared to high-educated women and women in the lowest 25(OH) vitamin D quartile had a higher risk of SGA offspring. In addition, low-educated women had a higher risk of SGA offspring (OR 1.95; 95% CI 1.20 – 3.14). This association decreased with 7% after adjustment for 25(OH) vitamin D (OR 1.88; 95% CI 1.16 – 3.04). In stratified analyses, adjustment for 25(OH) vitamin D resulted in a decrease in OR of about 17% in overweight women, and about 15% in women who conceived in wintertime.

Conclusions

25(OH) vitamin D appears to be a modifiable contributor to the association between low maternal education and SGA offspring, particularly in overweight women and women who conceived in the winter period. In those women, increasing the intake of vitamin D, either through dietary adaptation or supplementation in order to achieve the recommendation, could be beneficial.

INTRODUCTION

Small for gestational age (SGA) is strongly related to neonatal mortality[111] and adverse health outcomes in adult life. More specifically, SGA infants are at an increased risk for cardiovascular disease, type 2 diabetes mellitus, and psychomotor and intellectual impairment.[75,76] To limit these consequences, research in the epidemiology and causal factors underlying SGA is needed.

Socioeconomic status (SES) has been adversely associated with the risk of SGA offspring.[30,78,112,113] Compared to women of high socioeconomic status, those of low socioeconomic status gave birth to more SGA offspring, but these disparities have not been fully explained.[30] Low SES has no direct effect on SGA; it leads to unhealthy behaviour such as smoking, and a suboptimal diet. Such exposures might be the mediating variables in the relation between SGA and socioeconomic status.

Maternal vitamin D status has previously been associated with both socioeconomic status,[114-116] and SGA[117] and therefore appears to be a plausible mediating variable. Vitamin D is essential for fetal brain development, immunological functions, calcium homeostasis, and bone mineralization and therefore vital to fetal and infant development.[118] The fetus relies on the vitamin D stores of the mother so if the mother is deficient, so is the fetus.[115] Recently, it was shown that a vitamin D supplementation of 4000IU/day during pregnancy improved maternal vitamin D status throughout pregnancy and improved vitamin D status at birth in a randomized clinical trial.[119] 25(OH) vitamin D is the main circulating metabolite of vitamin D, and its concentration in serum reflects the vitamin D stores in humans.[120] In a small percentage, vitamin D comes directly from the diet, especially from fatty fish and fish oils, egg yolk, and liver, though vitamin D is mostly formed in skin by exposure to sunlight. For this reason, dark-skinned individuals are more prone to 25(OH) vitamin D deficiency than those with white skin, thus 25(OH) vitamin D may be a link to black-white disparities in adverse birth outcomes.[115] It is not clear whether 25(OH) vitamin D explains the association between adverse birth outcomes and socioeconomic disparities. As a low 25(OH) vitamin D concentration was found to be more common among low-educated women and 25(OH) vitamin D is important for fetal development, this vitamin might contribute to educational disparities in SGA.

The contribution of 25(OH) vitamin D to socioeconomic disparities in SGA may be affected by different factors. One factor is overweight, as 25(OH) vitamin D insufficiency is associated with overweight.[121,122] Low levels of 25(OH) vitamin D in overweight women have been attributed to multiple factors such as storage of vitamin D in adipose tissue[123] and also to decreased sun exposure because of limited mobility, and less hepatic synthesis of 25(OH) vitamin D.[124,125] Vitamin D deficiency has even been suggested to be a causal factor of obesity.[126] The second potential factor is seasonality. Since 25(OH) vitamin D is formed mostly by sun exposure, an insufficiency of 25(OH) vitamin D most likely occurs during winter[127] and the beginning of spring.[128] Maternal smoking is the third factor, because smoking reduces the concentration of 25(OH) vitamin D.[129,130] The exact mechanisms underlying disturbances of 25(OH) vitamin D in smokers are unclear,[131] but it has been suggested that low 25(OH) vitamin D was the consequence of an increased calcium release from resorbed bone in smokers,[129] or a lower dietary vitamin D intake.[132]

This study aimed firstly to investigate whether maternal first trimester 25(OH) vitamin D contributes to the association between maternal education and SGA, and secondly whether this contribution differs by overweight, season, and smoking. Data was available from Dutch pregnant women and their children who participated in a large population-based cohort study: the ABCD study. Other ethnic groups participating in this study were excluded from the present analysis, because of the large ethnic differences in maternal 25(OH) vitamin D,[115] and birth outcomes.[133,134]

METHODS

Study population and design

This study is part of the ABCD study, a population-based birth cohort study. Detailed information on the study design was published elsewhere.[43] In short, between January 2003 and March 2004, all pregnant women in Amsterdam, the Netherlands, were invited to participate at their first antenatal visit with their obstetric caregiver. 12 373 women were informed about the study, 8266 enrolled by returning the pregnancy questionnaire (response rate 67%). Fifty-three percent (4389 women) participated in the biomarker study and 4236 of these women had a reliable serum 25(OH) vitamin D at early pregnancy (mean gestational age 90.7 days (SD 19.7), no significant difference between vitamin D quartiles). The present study included women with a pregnancy duration of 24 weeks or more who gave birth to a live-born singleton and with data on all relevant study variables. Women of Dutch ethnicity (born in the Netherlands, with a mother born in the Netherlands as well) were selected for the present study, so finally there were 2274 participants with completed data. The study was approved by the Medical Ethical Committee of the participating hospitals and the Registration Committee of the Health Municipality of Amsterdam. All women gave written informed consent.

Dependent variable

Infants were defined as SGA if their birth weight was below the tenth percentile for gestational age of parity and sex specific references of the Perinatal Registration, the Netherlands (PRN).[60] Information on birth weight and gestational age at delivery was obtained from the Youth Health Care Registration at the Public Health Service in Amsterdam, and the PRN, which includes the national obstetric databases for midwives and gynaecologists, and the national neonatal database for paediatricians and neonatologists. Gestational age was either based on ultrasound, or on the timing of the last menstrual period (< 10%).

Independent variable

The number of years of education after primary school was obtained by questionnaire. Education was categorized as low (≤ 5 years of education after primary school), mid (6 - 10 years) and high (> 10 years). Education is the indicator most often used of SES and typically measured as years completed.[100]

Potential explaining factor

Maternal 25(OH) vitamin D was taken from a blood sample in a 9ml evacuated tube (Vacuette; Breiner BV, Alphen aan de Rijn, The Netherlands), which was sent to the Regional Laboratory of Amsterdam (either by courier or by overnight mail in special envelopes) for preparing by centrifugation (1600 g for 10 min at room temperature), and stored as 1 ml aliquots at -80°C until analysis. Thereafter, serum 25(OH) vitamin D was measured using an enzyme immunoassay method (OCTEIA AC-57F1 IDS Ltd, Boldon, UK). Reliability was checked using the HIL-index: serum specimens may contain Hb (H, haemolysis), bilirubin (I, icterus), and lipids (L, lipaemia) that can adversely impact clinical chemistry tests. When values for this dimensionless index were above 1400, 30 and/or 250 respectively, the data were considered unreliable. More information about the vitamin D measurement in our sample was described previously.[114] As there is a lack of consensus on the threshold of maternal 25(OH) vitamin D that defines sufficiency,[135] and 25(OH) vitamin D had a non-linear association with SGA, it was divided into quartiles.

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Covariables

Covariables, available from the pregnancy questionnaire, were maternal height (cm, continuous), and maternal age (15 – 24, 25 – 34, 35 – 44 years). Factors that possibly affect the 25(OH) vitamin D-contribution to the association between maternal education and SGA were overweight, season of blood sampling, and maternal smoking. Prepregnancy maternal height and weight were self-reported in the pregnancy questionnaire and used to compute prepregnancy BMI (weight (kg) divided by height squared (m^2)). Women with BMI > 25 kg/m^2 were classified as overweight. Season of blood sampling was dichotomized into summer (May-October) and winter (November – April). Smoking status during pregnancy was self-reported in the pregnancy questionnaire and was dichotomized (no or yes if the mother used 1 or more cigarettes per day).

Statistical analyses

General characteristics and characteristics according to 25(OH) vitamin D quartiles were tested with one-way ANOVA for continuous variables and Chi-square tests for categorical variables. The association between maternal education and SGA was examined using logistic regression analysis (reference group: high educational level). As 25(OH) vitamin D was significantly associated with both maternal education and SGA, the contribution of

25(OH) vitamin D in the association between maternal education and SGA was tested by additional adjustment for 25(OH) vitamin D in the basic model. Subsequently, the contribution of 25(OH) vitamin D was calculated with the formula: (OR basic model – OR 25(OH) vitamin D-adjusted model) / (1 – OR basic model)*100.[136] Basic models were adjusted for maternal age and height. To investigate whether the role of 25(OH) vitamin D differed by prepregnancy overweight, season, and/or maternal smoking, we repeated the analysis stratified by these three factors. All statistical analyses were performed using the Statistical Package of Social Sciences version 15.0 for Windows (SPSS Inc., Chicago, IL, USA). A p-value <0.05 was regarded as significant in all analyses.

RESULTS

Table 4.1 shows that the low-educated women had on average a shorter height, were younger, were more likely to be overweight and a current smoker compared to high-educated women. In addition, low-educated women had a lower early pregnancy 25(OH) vitamin D level (mean 60.09 nmol/L, SD 36.83) than high-educated women (mean 68.27 nmol/L, SD 27.15). Women in the lowest 25(OH) vitamin D quartile were primiparous less often, were on average less tall, and were younger. Furthermore, these women were more likely to have conceived in winter, to be smoking currently, and to be overweight.

In our sample, we observed a prevalence of 9.1% for SGA. Women in the lowest 25(OH) vitamin D quartile were more likely to give birth to SGA offspring (OR 1.57; 95% CI 1.03 – 2.39) after adjustment for maternal age, height and maternal education. In addition, the low-educated mothers were more likely to give birth to SGA offspring (OR 1.95; 95% CI 1.20 – 3.14). By adding 25(OH) vitamin D quartiles to the model, the association of maternal education on SGA decreased about 7% (Table 4.2). In addition, this association declines about 17% in overweight women and about 15% in women who conceived in winter, although in the latter the association between low educational level and SGA was not significant. In analyses stratified by smoking, the decreases in ORs after adjustment for 25(OH) vitamin D quartiles did not substantially differ between smokers and non-smokers.

Table 4.1. General characteristics by maternal education

		Maternal educational level			
	Total	High	Mid	Low	p-value*
	(n =2274)	(n = 1297)	(n = 811)	(n=186)	
Primiparous (%)	60.7	61.8	60.2	55.4	.27
Sex (% boys)	49.0	50.1	46.6	51.5	.24
Maternal height, cm (95% CI)	171.7 (171.4 – 171.9)	172.1 (171.7 – 172.4)	171.4 (171.0 – 171.9)	170.0 (169.1 – 170.9)	<.001
Maternal age, yr					<.001
15 – 24 (%)	4.3	4.1	59.2	36.7	
25 – 34	70.6	60.8	33.3	5.9	
35 – 44	25.1	55.4	38.2	6.3	
Overweight (% yes)	16.4	13.1	19.6	25.9	<.001
Season of blood sampling (% winter)	55.5	55.6	54.5	59.4	.51
Smoking (% yes)	6.6	2.4	7.6	34.3	<.001
25(OH)vitamin D concentration, nmol/L (95% CI)					<.01
8.5 – 48.2 (lowest quartile)	34.77 (31.01 – 35.54)	35.34 (34.32 – 36.36)	34.31 (32.93 – 35.69)	33.55 (31.37 – 35.73)	
48.3 – 65.4	57.15 (56.74 – 57.57)	57.12 (56.78 – 57.89)	56.98 (56.28 – 57.69)	56.56 (55.03 – 58.09)	
65.4 – 84.3	74.38 (73.94 – 74.82)	74.39 (73.80 – 74.97)	74.56 (73.84 – 75.27)	72.63 (70.39 – 74.86)	
84.3 – 284.6 (highest quartile)	105.32 (103.61 – 107.03)	104.28 (102.38 – 106.18)	105.22 (102.58 – 107.86)	116.97 (100.41 – 133.52)	

*p-values are based on one-way ANOVAs and Chi-square tests

Table 4.2. Association between SGA and maternal education

	SGA (%)	25(OH) D nmol/L mean (sd)	Basic model* OR (95% CI)	Basic model adjusted for 25(OH)D (quartiles)
Total (n=2274)	9.1			
Low	16.3	60.09 (36.83)	1.95 (1.20 – 3.14)	1.88 (1.16 – 3.04)
Mid	8.1	68.83 (28.14)	0.89 (0.64 – 1.22)	0.89 (0.65 – 1.23)
High	8.9	68.27 (27.15)	Reference	Reference
Overweight women (n=372)	6.5			
Low	18.6	49.80 (23.79)	4.62 (1.66 – 12.88)	4.00 (1.41 – 11.40)
Mid	3.8	58.31 (24.19)	0.70 (0.25 – 1.99)	0.68 (0.24 – 1.95)
High	5.9	62.66 (27.52)	Reference	Reference
Non-overweight women (n=1902)	9.7			
Low	15.4	63.68 (39.87)	1.57 (0.90 – 2.77)	1.53 (0.87 – 2.70)
Mid	9.2	71.51 (28.45)	0.94 (0.67 – 1.32)	0.95 (0.68 – 1.34)
High	9.3	69.11 (27.02)	Reference	Reference
Winter (November – April) (n=1260)	10.0			
Low	16.3	45.72 (22.75)	1.65 (0.88 – 3.09)	1.55 (0.82 – 2.92)
Mid	8.9	59.88 (25.60)	0.83 (0.55 – 1.27)	1.29 (0.55 – 1.28)
High	9.9	58.90 (25.37)	Reference	Reference
Summer (May – October) (n=1014)	8.1			
Low	16.4	81.45 (43.29)	2.48 (1.18 – 5.21)	2.48 (1.18 – 5.21)
Mid	7.4	79.57 (27.27)	0.98 (0.59 – 1.62)	0.98 (0.59 – 1.62)
High	7.7	50.06 (24.68)	Reference	Reference
Smoking women (n=150)	23.3			
Low	24.6	50.67 (38.11)	2.56 (0.73 – 8.95)	2.54 (0.72 – 8.31)
Mid	27.4	60.40 (33.24)	2.76 (0.83 – 9.20)	2.77 (0.83 – 9.26)
High	12.9	59.52 (22.79)	Reference	Reference
Non-smoking women (n=2124)	8.1			
Low	11.9	65.01 (35.04)	1.37 (0.73 – 2.57)	1.35 (0.72 – 2.54)
Mid	6.5	69.63 (27.59)	0.72 (0.50 – 1.02)	0.72 (0.50 – 1.02)
High	8.8	68.48 (27.22)	Reference	Reference

*Basic model adjusted for maternal height, and maternal age (categorical)

DISCUSSION

This study, examining the contribution of early pregnancy 25(OH) vitamin D to the association between maternal education and SGA, found that 25(OH) vitamin D explains about 7% of this association. 25(OH) vitamin D differs between maternal educational levels in overweight women and in women who were in early pregnancy in winter and in these women particularly 25(OH) vitamin D appears to be a considerable yet modifiable contributor to educational inequalities in risk of delivering SGA offspring.

To the best of our knowledge, this is the first study that examined the role of maternal 25(OH) vitamin D in the relation of maternal education to SGA. However, the relation of SGA to vitamin D was described previously. Comparable to Bodnar et al.[115] we found an increased risk of SGA at low 25(OH) vitamin D in early pregnancy. Other studies, examining the association between maternal 25(OH) vitamin D in the third trimester and infant birth weight found no association.[137-139] In addition, Hollis et al.[119] conducted a randomized, double-blind trial and found that vitamin D supplementation in the second and third trimester was not associated with birth weight. Recent evidence suggests that the growth trajectory of the fetus may be determined in early pregnancy,[140] though Brooke et al.[141] found among 126 Asian mothers living in Britain that supplementation with 1000 IU vitamin D starting in the third trimester reduced the risk of SGA. Vitamin D supplementation during pregnancy remains controversial and the choice to provide this should probably be more an individual decision.

25(OH) vitamin D has a biologically plausible role in fetal growth, regulating human chorionic gonadotropin expression and secretion in human synctiotrophoblast[142] and increasing placental sex steroid production.[143] Vitamin D might also play a role in fetal glucose usage because vitamin D is important in glucose/insulin metabolism[144] and can directly influence skeletal muscle and bone development through calcium homeostasis and transport.[115,145] In our sample, lower 25(OH) vitamin D levels were more common in pregnant women with a low educational level. This finding concords with Puri et al.[117] who examined healthy schoolgirls from two different socioeconomic strata in India, and with Olmez et al.[127] who examined healthy adolescents in Turkey. In contrast, others found no association between maternal education or occupation and 25(OH) vitamin D during pregnancy, but these were small study samples.[120,146]

In the present study the contribution of 25(OH) vitamin D to the association between maternal education and SGA was 7%. Furthermore, 25(OH) vitamin D explains about 17% of this association in overweight women. It is most likely that obesity results in low serum 25(OH) vitamin D, because of increased storage and sequestration of vitamin D in adipose tissue.[147] Therefore, the contribution of 25(OH) vitamin D might be more in obese women than in overweight women. Although the relation between maternal education and SGA was nonsignificant in women who conceived in winter, adjustment for 25(OH) vitamin D induced a 15% decrease in OR, indicating that 25(OH) vitamin D also affects the association between maternal education and SGA in these women.

A major strength of this study was not only the community-based prospective study design but also that analyses were based on a sample of women from homogenous descent. Although this homogenous sample might limit the external validity of our results, it may have diminished confounding effects of ethnicity and skin colour. Besides several strengths, some limitations warrant to be mentioned. Firstly, the statistical method hinges on causal assumptions, while causality can not be proven. Therefore, we have to point out that results can not be interpreted as causal effects and the percentages mentioned in the results should not be interpreted as precise quantities. On the other hand, the effect of vitamin D is based on a plausible pathophysiologic mechanism, so causality is plausible. Secondly, 25(OH) vitamin D was assessed during early pregnancy, while the majority of past studies examined the effect of vitamin D in the 3rd trimester of pregnancy, when fetal growth velocity is greatest.[115] As mentioned previously, evidence indicates that fetal growth trajectory in late gestation is determined much earlier, most likely in early pregnancy.[140] However, further research is required to improve the understanding of the relation of 25(OH) vitamin D on several points in time to SGA. Thirdly, confounding can not fully be excluded. Unmeasured confounders, like other vitamins, and micronutrients may have biased our results as 25(OH) vitamin D might reflect a healthier lifestyle in high-educated women in general. Detailed analyses of overall micronutrient profile in relation to birth outcomes in the ABCD study are planned. Finally, the low response rate might have caused bias. It was expected that low-educated women with a less healthy lifestyle are less likely to participate, which could have underestimated our results. For the first time the contribution of vitamin D to educational inequalities in adverse birth outcomes was assessed. Future studies should explore underlying factors of the contribution of 25(OH) vitamin D, while taking into account the influence of dietary intake and sun exposure. It is also recommended to measure biomarkers of the vitamin D endocrine system such as parathyroid hormone and considering fetal growth during pregnancy with ultrasound measurements.

CONCLUSION

Our results show that 25(OH) vitamin D contributes to the association between maternal education and SGA, in particular in overweight women and women who conceived in winter. The Health Council of The Netherlands recommends a higher intake of vitamin D for pregnant women than for non-pregnant women, although the benefits have been doubted by prenatal care providers. In addition, in a more southern geographic latitude in Europe an intake of 800IU/day is recommended for both pregnant and non-pregnant women, while the Institute of Medicine's Dietary Reference Intakes (IOM 2010) recommends an intake of

600 IU/day for both pregnant and non-pregnant women. Our results suggest that an intake according to the recommendation will help reduce the risk of delivering SGA offspring in low-educated women, at least in those with overweight and those who conceived in winter. Further research into the benefits of universal supplementation versus individual screening and treatment seems worthwhile.