Irish Journal of Medical Science (1971 -)
https://doi.org/10.1007/s11845-019-02078-5

ORIGINAL ARTICLE

Association between vitamin D status in early pregnancy and atopy in offspring in a vitamin D deplete cohort

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Received: 20 December 2018 / Accepted: 3 August 2019

Abstract

Background Vitamin D status may play a role in the development of atopic diseases due to its action on lung development and immune system development and function.

Aims Our objective was to assess whether 25-hydroxyvitamin D (25OHD) levels in maternal blood in pregnancy were associated with atopy in children.

Methods We analysed 279 mother-child pairs from the ROLO study conducted in Dublin, Ireland. Serum 25OHD was measured at 13 and 28 weeks of pregnancy. Development of childhood atopy was self-reported by mothers at follow-up appointments at 6 months, 2 years or 5 years. Logistic regression analysis was used to evaluate associations between maternal 25OHD status and development of atopy.

Results The mean (SD) 25OHD levels in early and late pregnancy were 41.9 (19.2) nmol/L and 40.2 (21.6) nmol/L, respectively. Maternal 25OHD status in early pregnancy, but not in late pregnancy, was associated with a reduced risk of atopy at 2 years (OR 0.972, CI 0.946–0.999). In early pregnancy, those with serum 25OHD levels < 30 nmol/L compared with those with 25OHD > 50 nmol/L had significantly greater risk of developing atopy at 2 years (OR 4.76, CI 1.38–16.47).

Conclusions The development of childhood atopy may be associated with maternal vitamin D deficiency in early pregnancy among a cohort of women at risk of vitamin D deficiency. Further research is required to explore the relationship between vitamin D and atopy, particularly among women with poor vitamin D status, and whether supplementation should be prioritised in early pregnancy to reduce childhood atopy.

Keywords Atopic disease · Childhood · Longitudinal study · Pregnancy · ROLO · Vitamin D

Introduction

Levels of atopic diseases have risen considerably in recent years, especially in children [1]. Fourteen percent of children suffer from asthma worldwide [1] and the prevalence of eczema in children is approximately 20% [2]. Atopic diseases such as asthma and eczema place a large financial burden on healthcare systems, and they also negatively affect the patient's quality of life [3]. While treatments are advancing, there is currently no cure.

Maternal vitamin D status has been identified as a biologically plausible cause for this rise in atopic diseases due to the role of vitamin D in in utero lung development and in immune system development and function [4]. There are, however, conflicting results as some studies have reported a relationship between fetal serum vitamin D at the time of birth and atopy development in offspring [5–7] while others have found no relationship [8]. Moreover, one study reported that higher maternal 25-hydroxyvitamin D (25OHD) was associated with increased risk of atopic diseases in offspring [9].

Some studies reporting a positive relationship have relied on food frequency questionnaires to determine maternal intake of vitamin D [5, 10]. As dietary intake is not the only source of vitamin D, this is not a reliable measure. Since

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Published online: 29 August 2019

25OHD is a major circulating metabolite that reflects the sum of vitamin D produced cutaneously and vitamin D derived from natural foods, fortified foods, and supplements, it is considered the gold standard when determining vitamin D status [11].

Vitamin D deficiency is common due to reliance on exposure to ultra-violet B (UVB) radiation via sunlight to generate vitamin D_3 production. This is a particular issue in countries at latitudes above 42° north, such as Ireland, as endogenous production of vitamin D ceases from November to March [12]. Pregnant women who gestate through winter have lower serum 25OHD levels than those who gestate through summer [13, 14]. During these months, there is a reliance on intake of vitamin D from dietary sources and through the use of supplements. Reduced sun exposure due to more time spent indoors and an increase in the use of sunscreen also contribute to inadequate vitamin D status.

The reference nutrient intake (RNI) for vitamin D was recently reviewed by the scientific advisory committee on nutrition (SACN) and concluded that 10 μg/400 IU per day is recommended for the general population including pregnant and lactating women [15]. Dietary intakes of vitamin D among pregnant women are poor with intakes of 2.0, 1.9 and 2.1 μg/day during trimester 1, 2 and 3, respectively [16]. Despite vitamin D supplementation of 5 μg/200 IU being recommended at a national level in Ireland [17], 26% of women are not compliant [18].

Our objective was to assess whether maternal 25OHD status in early or late pregnancy was associated with atopy in children at 6 months, 2 years and 5 years. We hypothesised that low maternal 25OHD status would be associated with increased risk of atopy.

Methods

Study design and setting

This was a prospective study of 288 pregnant women originally recruited as part of the ROLO (Randomised cOntrol trial of LOw glycaemic index diet versus no dietary intervention to prevent recurrence of fetal macrosomia) study at the National Maternity Hospital (Dublin, Ireland) [19]. The ROLO study was a randomised controlled trial of a low gylcaemic index (GI) dietary intervention versus usual care involving 800 secundigravida women with a history of macrosomia, with the primary objective being a reduction in birthweight [19]. In brief, the low GI diet resulted in lower dietary glycaemic load but was not associated with birthweight. The mean birthweight of this cohort was 4.06 kg. Significant maternal benefits were observed in the intervention compared with the control group in terms of less gestational weight gain (12.2 vs. 13.7 kg, $p < 0.05$) and reduced glucose intolerance (21 vs. 28%, $p < 0.05$) [19]. No differences in 25OHD status were noted between the intervention and control groups. The study was conducted according to the guidelines laid down in the Declaration of Helsinki with institutional ethics approval from the National Maternity Hospital, Ireland, and informed, written maternal consent.

Subject selection

Study participants were recruited to the study at their first antenatal consultation (at about 13 weeks' gestation). They were required to have healthy, singleton pregnancies with no intrauterine growth abnormalities. Women were excluded from the study if they had an underlying medical condition, previous or current diabetes, were less than 18 years of age or were unable to provide full informed consent.

For this analysis, the following study criteria were applied; participants must have provided a blood sample during early or late (28 weeks' gestation) pregnancy. They were also required to have participated in subsequent mother/child follow-up at 6 months, 2 years or 5 years during which information on atopy development was obtained. Infants and children were eligible for inclusion in each follow-up to a maximum age of 9 months for first post-natal follow-up, 2 years and 6 months for second post-natal follow-up and 5 years and 6 months for third follow-up. Maternal informed written consent was obtained at each follow-up appointment.

Data collection

All women had weight and height recorded at the first antenatal consultation. Participants were weighed by the research team in light clothing using a SECA weighing scales (SECA GmbH & Co. Kg. Germany) to the nearest 0.1 kg, and height was measured without shoes to the nearest 0.1 cm using a wall mounted stadiometer. Information on maternal education level, smoking status and ethnicity were collected from participants' medical chart. Maternal education level was recorded as a marker of socioeconomic status. Fasting maternal blood samples were taken in early pregnancy and in late pregnancy. At delivery, infant birth weight was recorded.

All participants who returned for follow-up at 6 months, 2 years and 5 years were requested to complete questionnaires prior to the appointment. The questions on lifestyle habits were taken from the SLAN 2007 questionnaire (Survey of Lifestyle, Attitudes and Nutrition in Ireland) [20]. It contained questions on infant health including whether their child had experienced asthma or eczema. The question was phrased as "does your child have any ongoing problems, tick all that apply", followed by a list including asthma and eczema. If the participants answered "yes" to having either asthma or eczema, they were recorded as positive atopy; if they answered no, then they were recorded as negative atopy. The

questionnaires also contained questions relating to breastfeeding and breastfeeding duration.

Laboratory analysis

All blood samples were centrifuged at 3000 rpm for 10 min and serum sub-aliquoted and stored at − 80 °C until analysis. Serum 25OHD concentration was determined using the Elecsys Vitamin D Total (Roche Diagnostics GmbH, Mannheim, Germany) automated competitive binding protein assay, as previously described [21]. The coefficients of variation (CV) for the 25OHD assay determined at assay verification were as follows: inter-assay CV, 8.9% at a concentration of 49.5 nmol/L and 3.7% at 103 nmol/L (intra-assay CV, 2.9% and 1.4% respectively).

Statistical analysis

Data was assessed for normality using the Kolmogorov-Smirnov test; the 25OHD analytes were non-normally distributed. Results were expressed as mean ± standard deviation or median (interquartile range). Baseline characteristics were compared between positive and negative atopy groups using independent sample *t* tests (BMI, age at delivery, birth weight and breastfeeding duration), chi-square tests (ethnicity, initiated breastfeeding, education, smoking status) and Mann-Whitney *U* tests (25OHD). Data was analysed by gestation (early and late pregnancy) for each of the follow-up time points (6 months, 2 years, 5 years) and cumulative incidence that combined results from each of the time points.

Analysis with binary logistic regression was used to investigate if serum 25OHD level was associated with the risk of developing atopy at any of the time points. Analysis of 25OHD status was further stratified into groups according to the Institute of Medicine (IOM) classification of 25OHD, in order to assess if the risk of developing atopy was increased in those considered at risk of deficiency (25OHD < 30 nmol/L) or potentially at risk of inadequacy (25OHD between 30 and 50 nmol/L) compared with those considered vitamin D sufficient (25OHD > 50 nmol/L) [22]. Adjusted models included variables that were chosen a priori, based on the literature and variables that are typically controlled for in a heterogeneous population of mothers and children (maternal age, BMI, ethnicity, smoking, education, intervention study group, breastfeeding duration, birth weight, infant sex).

Results

Of the 288 participants who provided an early pregnancy blood sample, 250 attended follow-up at 6 months, 2 years or at 5 years. Of the 298 participants who provided a late pregnancy blood sample, 258 attended a follow-up at 6 months, 2 years or 5 years.

Maternal BMI was 26 ± 4.3 kg/m^2, 99% were Caucasian and 1.4% reported smoking during pregnancy (Table 1). The average birthweight was 4.09 ± 0.45 kg, and 61% reported ever breastfeeding the participant infant. There were no significant differences in the mother or infant characteristics between those who developed atopy in the first 5 years of life and those that did not.

Two hundred seventy-nine subjects completed the question on atopy at 6 months, 2 years or 5 years. Positive atopy was reported in 58/279: $n = 16$ at 6 months, $n = 34$ at 2 years and $n = 23$ at 5 years, and cumulatively $n = 58$ between 6 months and 5 years. Fourteen participants had a diagnosis of atopy at 2 or more time points.

On unadjusted Mann-Whitney *U* tests, no differences were observed in 25OHD status in early or late pregnancy between those who developed atopy in the first 5 years of life and those who did not (Table 1).

On binary logistic regression, maternal 25OHD in early pregnancy, but not in late pregnancy, was associated with a marginally reduced risk of atopy at 2 years, after adjustment for known confounders including maternal age at delivery, BMI, ethnicity, smoking status, education, study group, breastfeeding duration, birth weight and infant sex (OR 0.972, CI 0.946–0.999) (Table 2). In early pregnancy, those with serum 25OHD levels of < 30 nmol/L compared with those with 25OHD > 50 nmol/L had a greater risk of developing atopy at 2 years (OR 4.760, CI 1.376–16.465) (Table 3).

Discussion

Summary of main findings

Higher maternal serum 25OHD level in early pregnancy was associated with a significantly lower risk of atopy in children at 2 years of age. Those in early pregnancy with serum 25OHD levels below 30 nmol/L compared with those with serum 25OHD levels above 50 nmol/L had greater risk of the child experiencing atopy in the first 2 years of life.

The IOM 2011 Report on "Dietary Reference Intakes for Calcium and Vitamin D" specified both vitamin D intake requirements and corresponding serum 25OHD values [11]. The corresponding serum 25OHD level for the estimated average requirement (EAR) for total daily intake of vitamin D is 40 nmol/L; the corresponding serum 25OHD level for the recommended daily allowance (RDA) that would meet the intake requirement for 97.5% of the population is 50 nmol/L; and the corresponding serum 25OHD level for those deemed to be at "risk of deficiency" is < 30 nmol/L [11, 23]. Frequently misrepresented, this interpretation has recently been reemphasised [24]. In our study, the average

Table 1 Characteristics of mother and infants

	Positive atopy ($n = 58$)	Negative atopy ($n = 221$)	p value
Age at delivery (mean ± SD)	33.6 ± 4	33.2 ± 3.8	0.909
BMI at booking (mean ± SD)	26.0 ± 4.5	26.1 ± 4.3	0.542
Birth weight (mean ± SD)	4129 ± 454	4076 ± 453	0.427
Breastfed yes/no (n (%))			
No	25 (43.1)	84 (38.0)	
Yes	33 (56.9)	137 (62.0)	0.479
Breastfeeding duration in weeks [Median (IQR)]	2.17(0–31.5)	6.52 (0–30.4)	0.374
Ethnicity (n (%))			
Caucasian	57(98.3)	219(99.1)	
Other	1 (1.7)	2 (0.9)	0.590
Completed third level education (n (%))			
No	21 (40.4)	83 (41.3)	
Yes	31 (59.6)	118 (59.6)	0.905
Baseline smoker (n (%))			
No	58 (100)	216 (98.2)	
Yes	0	4 (1.8)	0.301
25OHD early pregnancy (median (IQR))			
6 months	40.5 (30.5–62.5)	42 (28.8–55)	0.831
2 years	38 (22–51)	41 (29–53.5)	0.138
5 years	36.5 (21.5–54)	39 (27.5–6)	0.676
Cumulative incidence by 5 years	39 (27–54)	40 (27–54)	0.618
25OHD late pregnancy (median (IQR))			
6 months	40.6 (23.7–70.2)	34.6 (25.1–67.7)	0.329
2 years	38.0 (23.2–55.6)	32.92 (25.9–52.2)	0.872
5 years	29.6 (22.1–61.1)	39.87 (26.4–53.1)	0.365
Cumulative incidence by 5 years	32.6 (23.7–60.6)	35.82 (25.7–53.1)	0.888

p values were calculated by using independent sample t tests, chi-squared tests and Mann-Whitney U tests

serum 25OHD level in both early and late pregnancy was equivalent to the EAR at 41.9 nmol/L and 40.2 nmol/L; but, 25OHD was below 30 nmol/L in 29% during early pregnancy and in 37% during late pregnancy. About one-third would be deemed at risk for deficiency.

Comparison with other studies

Significant interest has developed in whether maternal 25OHD has a role in childhood atopy. Two separate randomised controlled trials (RCTs) were conducted in order to test whether supplementation with vitamin D in pregnancy reduced the prevalence of asthma and other allergic diseases in the offspring [8, 25]. The $COPSAC_{2000}$ study tested whether maternal pre-natal supplementation with vitamin D 2400 IU/day from 28 weeks' gestation, in addition to pre-natal multivitamin containing 400 IU/day, could reduce asthma or other atopic diseases including eczema in the first 7 years of life; the control group received the pre-natal vitamin only. There was no significant benefit with respect to occurrence of asthma or eczema. Fetal cord blood serum 25OHD level below 50 nmol/L compared with serum 25OHD above 100 nmol/L was associated with a 4-fold increase in the risk of developing troublesome lung symptoms [8]. The VDAART study assessed whether maternal prenatal supplementation with vitamin D 4000 IU/day from 14 weeks' gestation in addition to pre-natal multivitamin containing 400 IU/day daily could prevent asthma or recurrent wheeze in early childhood; the control group received a placebo along with pre-natal multivitamin. There was no benefit with respect to reduction in incidence of asthma or recurrent wheeze in children up until age 3 years [26].

Both studies recruited women at high-risk of having a child with atopy, but they were recruited into the study irrespective of their vitamin D status. Both studies' populations were vitamin D replete; mean serum 25OHD in $COPSAC_{2000}$ cohort was 77.4 nmol/L in both the intervention and control groups; and mean serum 25OHD in VDAART was 58.3 nmol/L and 56.3 nmol/L in the intervention and control groups respectively. This may partly explain why the RCTs failed to observe a

Table 2 Associations between maternal and fetal biomarkers and atopic disease outcomes

	Atopy at 6 months				Atopy at 2 years				Atopy at 5 years				Atopy overall			
	Unadjusted		Adjusted¶		Unadjusted		Adjusted¶		Unadjusted		Adjusted¶		Unadjusted		Adjusted¶	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
25OHD early pregnancy	1.005	0.979–1.032	1.006	0.973–1.040	0.985	0.963–1.077	0.972*	0.946–0.999	0.998	0.973–1.023	1.013	0.986–1.041	0.998	0.982–1.014	1.000	0.982–1.018
25OHD late pregnancy	1.017	0.992–1.042	1.014	0.984–1.046	1.003	0.986–1.021	0.975	0.975–1.017	0.994	0.972–1.016	0.995	0.971–1.020	1.005	0.991–1.018	0.999	0.984–1.015

*$p \leq 0.05$

¶ Adjusted for maternal age, BMI, ethnicity, smoking, education, intervention study group, breastfeeding duration, birth weight, infant sex

Values were found using binary logistic regression

reduction in atopy in the offspring. The cohort in our study were much more likely to be vitamin D deplete with one-third having serum 25OHD below 30 nmol/L. This finding is in keeping with current Irish data which demonstrates that approximately 1 in 4 Irish adults have vitamin D < 30 nmol/L [27]. The supplementation period in the RCTs, commencing at 14 weeks and 24 weeks, may have been too late to demonstrate an effect; this was recognised as a limitation in the VDAART study [26]. Development and maturation of the immune system and development of the lung occur early in the first trimester [4, 28], ensuring vitamin D adequacy during the early stage of pregnancy, and possibly in the preconception period, could facilitate these functions. Our study supports this theory, but future research with clearly defined outcomes is required to determine if this effect is true. The editorial about both RCTs suggested strongly that the use of high-dose vitamin D supplements in RCTs should be reconsidered in view of the absence of benefit and that the follow-up period should be extended due to difficulties in diagnosing childhood atopy [29].

Findings from our study are consistent with observational studies, which have reported that vitamin D in pregnancy may influence the development of atopy in offspring [5–7, 30]. Although results in the literature of the association between atopy and vitamin D status are conflicting, many of these studies were carried out in populations where the risk of vitamin D deficiency is low making it difficult to compare to the current study [5–7, 10, 30].

To our knowledge, our study is the first study to report an association between maternal 25OHD status in early pregnancy and atopy at 2 years. A Spanish study in a vitamin D replete cohort (mean 25OHD, 75.6 ± 28 nmol/L) found that 25OHD status in early pregnancy was associated with a reduced risk of respiratory tract infection in the first year of life but was not associated with asthma when children were followed up between 4 and 6 years [31]. Similarly we did not find an association between maternal 25OHD and atopy at 5 years. In a prior study of pre-term infants with a high prevalence of low 25OHD (< 30 nmol/L), we found an association between vitamin D status and acute respiratory morbidity [32].

The Southampton Women's Study found that 25OHD status in late pregnancy (at about 35 weeks) was not associated with development of atopy or asthma in offspring [33]. The current study also found no associations between 25OHD status in late pregnancy and the development of atopy in childhood. Goldring et al. [34] examined vitamin D supplementation in late pregnancy; more than half the participants had 25OHD levels below 25 nmol/L. Participants were randomised to one of three intervention arms: 800 IU of vitamin D to be taken daily from 27 weeks' gestation, a once off bolus containing vitamin D 200000 IU at 27 weeks' gestation or no supplementation. The study did not find evidence of protective effect of the interventions on wheeze, allergic

Table 3 Associations between those at risk of deficiency (25OHD < 30 nmol/L) and at risk of inadequacy (25OHD 30–50 nmol/L) of 25OHD and atopic disease outcome compared with those sufficient (25OHD > 50 nmol/L)

	Atopy at 6 months				Atopy at 2 years				Atopy at 5 years				Cumulative incidence by 5 years			
	Unadjusted		Adjusted¶		Unadjusted		Adjusted¶		Unadjusted		Adjusted¶		Unadjusted		Adjusted¶	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
25OHD early pregnancy																
< 30 nmol/L	0.776	0.173–3.479	0.883	0.143–5.45	2.148	0.826–5.584	4.760*	1.376-16.465	1.200	0.336–4.288	0.428	0.084–2.166	1.363	0.617–3.011	1.548	0.610–3.930
30–50 nmol/L	1.257	0.384–4.112	0.1962	0.226–4.094	0.810	0.294–2.234	1.247	0.345–4.505	1.229	0.359–4.213	0.994	0.226–3.718	1.172	0.549–2.503	1.326	0.558–3.155
> 50 nmol/L	Reference value															
25OHD late pregnancy																
< 30 nmol/L	0.540	0.153–1.096	0.794	0.177–3.569	1.280	0.494–3.320	1.881	0.624–5.676	1.754	0.581–5.298	1.725	0.503–5.914	0.975	0.473–2.010	1.373	0.596–3.166
30–50 nmol/L	0.372	0.87–1.593	0.268	0.044–1.636	1.048	0.386–2.850	0.645	0.190–2.189	0.606	0.159–2.305	0.625	0.133–2.941	0.596	0.271–1.310	0.499	0.199–1.251
> 50 nmol/L	Reference value															

*$p \leq 0.05$

¶Adjusted for maternal age, BMI, ethnicity, smoking, education, intervention study group, breastfeeding duration, birth weight, infant sex

Values were found using binary logistic regression

disease or lung function when children were followed up to 3 years [34]. Based on research to date, 25OHD status in late pregnancy does not appear to be associated with atopy development in offspring [33], and supplementation during this period does not seem to have a protective effect [34].

Strengths and limitations

This study has many strengths including the collection of blood samples at two separate time points and the measurement of 25OHD in serum which is more reliable compared with measuring dietary intake [35]. Three follow-up appointments were carried out at 6 months, 2 years and 5 years; this allowed us to investigate if maternal 25OHD was associated longitudinally with atopy development across early childhood.

This study has limitations worthy of consideration: firstly, the missing information on family history of atopy; secondly, the incidence of atopy was self-reported by the mothers which may be open to bias and due to small numbers the incidence of asthma or eczema were grouped together. The association between 25OHD status in early pregnancy and atopy at 2 years did not persist to 5 years. There are a number of possible explanations for this: children might outgrow atopic disease as eczema typically develops in children during the first 2 years of life; however, those that do usually do so around 10–12 years [36, 37]. Due to the nature of this research, the effect may have been lost as not all participants who attended follow-up at 2 years attended at 5 years.

Conclusions and recommendations for future research

In conclusion, the development of childhood atopy may be associated with maternal vitamin D status in early pregnancy. Children whose mothers are at risk of vitamin D deficiency (25OHD < 30 nmol/L) in early pregnancy may be at increased risk of developing atopy compared with those with adequate status (25OHD > 50 nmol/L). Further research is required to explore the relationship between vitamin D and atopy, particularly among women at risk of vitamin D deficiency, and whether targeted vitamin D supplementation to those at risk should be recommended prior to or during pregnancy in order to reduce development of childhood atopy.

Acknowledgements This study was supported by the Health Research Board Ireland and the Health Research Centre for Health and Diet Research.

Funding information This study was financially supported by the European Union's Seventh Framework Programme (FP7/2007-2013), project EarlyNutrition under grant agreement no. 289346

Compliance with ethical standards

The study was conducted according to the guidelines laid down in the Declaration of Helsinki with institutional ethics approval from the National Maternity Hospital, Ireland, and informed, written maternal consent.

Conflict of interest The authors declare that they have no conflicts of interest.

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