The Journal of Maternal-Fetal & Neonatal Medicine

ISSN: 1476-7058 (Print) 1476-4954 (Online) Journal homepage: http://www.tandfonline.com/loi/ijmf20

Vitamin D status in pregnant women with asthma and its association with adverse respiratory outcomes during infancy

Megan E. Jensen, V. E. Murphy, P. G. Gibson, J. Mattes & C. A. Camargo Jr.

To cite this article: Megan E. Jensen, V. E. Murphy, P. G. Gibson, J. Mattes & C. A. Camargo Jr. (2018): Vitamin D status in pregnant women with asthma and its association with adverse respiratory outcomes during infancy, The Journal of Maternal-Fetal & Neonatal Medicine, DOI: 10.1080/14767058.2017.1419176

To link to this article: https://doi.org/10.1080/14767058.2017.1419176

Published online: 05 Jan 2018.

THE JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE, 2018
https://doi.org/10.1080/14767058.2017.1419176

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Vitamin D status in pregnant women with asthma and its association with adverse respiratory outcomes during infancy

Megan E. Jensen[a*], V. E. Murphy[a*], P. G. Gibson[b,c], J. Mattes[a,d] and C. A. Camargo, Jr.[e]

[a]Priority Research Centre Grow Up Well, University of Newcastle and Hunter Medical Research Institute, Newcastle, Australia; [b]Department of Respiratory and Sleep Medicine, John Hunter Hospital, Newcastle, Australia; [c]Priority Research Centre for Healthy Lungs, University of Newcastle and Hunter Medical Research Institute, Newcastle, Australia; [d]Respiratory Department, John Hunter Children's Hospital, Newcastle, Australia; [e]Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

ABSTRACT

Background: Vitamin D may influence pregnancy and infant outcomes, especially infant respiratory health. This study aimed to examine vitamin D status in pregnant women with asthma, and whether higher vitamin D levels are associated with fewer adverse respiratory outcomes in their infants.

Methods: Pregnant women with asthma, recruited from John Hunter Hospital Newcastle Australia (latitude 33°S), had serum total 25-hydroxyvitamin-D (25(OH)D) measured at 16 and 35 weeks gestation. Infant respiratory outcomes were collected at 12 months by parent-report questionnaire. Mother–infant dyads were grouped by serum 25(OH)D during pregnancy: 25(OH)D $<$ 75 nmol/L (at both time-points) versus 25(OH)D $\geq$ 75 nmol/L (at one or both time-points).

Results: In 52 pregnant women with asthma, mean serum 25(OH)D levels were 61 (range 26–110) nmol/L at 16 weeks, and 65 (range 32–116) nmol/L at 35 weeks, gestation. Thirty-one (60%) women had 25(OH)D $<$ 75 nmol/L at both time-points; 21 (40%) had 25(OH)D $\geq$ 75 nmol/L at one or both time-points. Maternal 25(OH)D $<$ 75 nmol/L during pregnancy was associated with a higher proportion of infants with "wheeze ever" at 12 months, compared with 25(OH)D $\geq$ 75 nmol/L (71 versus 43%, $p = .04$). Infant acute-care presentations (45 versus 13%, $p = .02$) and oral corticosteroid use (26 versus 4%, $p = .03$) due to "asthma/wheezing" were higher in the maternal group with 25(OH)D $<$ 75 nmol/L, versus $\geq$75 nmol/L.

Conclusions: Most pregnant women with asthma had low vitamin D status, which persisted across gestation. Low maternal vitamin D status was associated with greater risk of adverse respiratory outcomes in their infants, a group at high risk of developing childhood asthma.

ARTICLE HISTORY
Received 30 August 2017
Revised 16 November 2017
Accepted 15 December 2017

KEYWORDS
Vitamin D; pregnancy; asthma; infant

Introduction

Low vitamin D status (e.g. circulating 25-hydroxyvitamin D (25(OH)D) $<$ 75 nmol/L) affects most women during pregnancy, with average levels ranging from 42 to 72 nmol/L in the western Pacific region [1], and can continue up to 12 months post-partum, regardless of season or supplementation [2]. Although vitamin D levels $<$75 nmol/L have been reported in adults with asthma and linked to worse asthma outcomes [3,4], it is unknown whether women with asthma have low vitamin D levels during pregnancy. Given the infant is entirely reliant on maternal vitamin D *in utero*, with cord blood 25(OH)D levels largely determined by maternal levels at term [1], vitamin D status during pregnancy has the potential to influence both maternal and infant outcomes.

Low vitamin D has been associated with poor perinatal outcomes, including gestational diabetes, preeclampsia, preterm birth, and low birth weight [5–7]. Furthermore, vitamin D exerts immunomodulatory effects in many tissues throughout the body; this may be important in conditions associated with altered immune function and localised inflammation, such as asthma. Both maternal and cord blood 25(OH)D levels are inversely associated with risk of respiratory infections in the first 3 months of life and preschool wheeze [8,9]. Thus, vitamin D has potential to influence the future respiratory health of offspring.

Infants born to women with asthma have a high risk for poor respiratory outcomes in early life, including bronchiolitis [10], persistent wheeze [11], and asthma [12,13]. However, infant health may be

CONTACT Megan E. Jensen megan.jensen@newcastle.edu.au University of Newcastle, University Drive, Callaghan, New South Wales, Australia
*These authors contributed equally to this publication.

influenced via manipulation of the prenatal environment, including nutritional status. Our group has previously demonstrated that optimised asthma management during pregnancy reduces the odds of recurrent bronchiolitis in infants [14]. Here, we examine if low vitamin D status during pregnancy in women with asthma is associated with a lower prevalence of adverse respiratory outcomes in their infants.

We hypothesise that persistently low vitamin D status (<75 nmol/L) is common in women with asthma during pregnancy and associated with adverse respiratory outcomes in their offspring. The aims of this study were to: (i) assess the vitamin D status of pregnant women with asthma; and (ii) to compare the proportion of infants experiencing adverse respiratory outcomes in the first 12 months of life, by maternal vitamin D status during pregnancy.

Materials and methods

Study design

This is a secondary analysis of a randomised controlled trial (RCT) of asthma management during pregnancy [15], with longitudinal follow-up of their infants during the first 12 months of life. The study was approved by the Hunter New England Human Research Ethics Committee (#07/02/21/3.06).

Population

Pregnant women aged ≥18 years, with physician-diagnosed asthma, between 12 and 20 weeks gestation, were recruited from John Hunter Hospital, Newcastle, Australia (latitude 33°S) [15]. Participants were eligible if they had used inhaled therapy (β_2-agonist, inhaled corticosteroids [ICS]) in the past year, and ineligible if they used more than three courses of oral corticosteroids (OCS) in the past 12 months. As previously described [15], women were randomised before 22-week gestation to either: (i) fractional exhaled nitric oxide (FENO)-guided asthma management, where asthma maintenance medication dose was altered according to FENO and symptoms; or (ii) the clinical guidelines-based asthma management group, where medications were altered according to asthma symptoms. Both groups were followed monthly during pregnancy. Infants were followed up during the first 12 months of life [14].

Clinical assessment

Maternal height and weight were recorded at baseline and body mass index (BMI, kg/m^2) calculated. Weight was collected at subsequent visits and gestational weight gain calculated and compared to recommended guidelines [16]. Smoking status was determined by participant report and confirmed by exhaled carbon monoxide (≥10 ppm, piCO Smokerlyzer Breath CO Monitor, Bedfont, UK) and urinary cotinine measurement (≥level 5 or 2840 nmol/L, Nicalert, NYMOX, Saint-Laurent, Quebec, Canada). A nonfasting blood sample was collected from a subset of women, at approximately 16 and 35 weeks gestation. Serum aliquots were stored at −80C until batch analysis of total 25(OH)D. Asthma treatment was selfreported throughout the study. Use of nutritional supplements was assessed from antenatal records.

Outcome measurement

The incidence and frequency of adverse infant respiratory outcomes, including wheeze, bronchiolitis and viral infections, and any related acute-care presentations (emergency department/unscheduled general practitioner visit), hospital admissions and medication use (ICS, OCS, and bronchodilators), were captured via administration of a validated parental-report questionnaire at 12 months of age [17].

Vitamin D measurement

Serum total 25(OH)D (comprised of 25(OH)D_2 and 25(OH)D_3) was quantified using the Abbott Architect assay (Abbott Park, IL), an enzyme-linked immunosorbent assay, at Massachusetts General Hospital, Boston, MA. Intra- and interassay coefficients of variation were <10%. Based on Endocrine Society guidelines for vitamin D status [18], serum 25(OH)D values were dichotomised at 75 nmol/L. Mother–infant pairs were grouped by maternal 25(OH)D level during pregnancy: (i) 25(OH)D ≥ 75 nmol/L at one or both gestational time-points; versus (ii) 25(OH)D < 75 nmol/L at both time-points.

Analysis

Statistics were performed using Stata version 11.1 (Stata Corp LP, College Station, TX). Two-sided $p < .05$ were considered statistically significant. Results are presented as mean (SD) or median [IQR], analysed using Student's *t*-test or Wilcoxon's rank-sum test, as appropriate. Proportions were analysed using X^2-test.

Results

There were 52 mother–infant pairs with serum 25(OH)D measurements for both time-points during

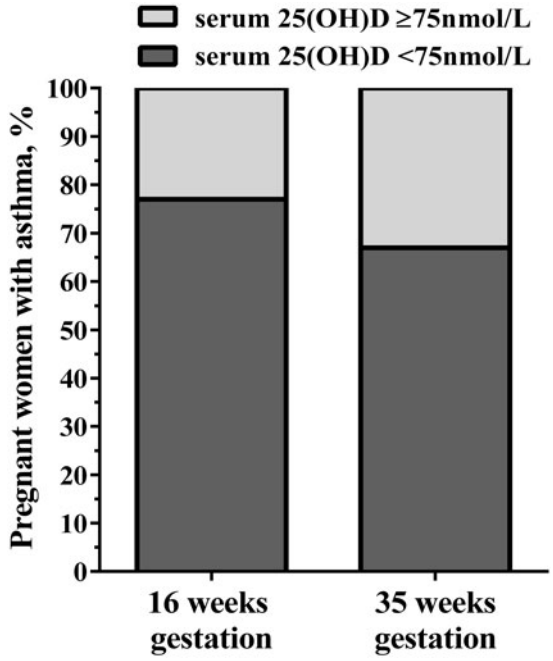

Figure 1. Maternal serum 25(OH)D < 75 nmol/L during pregnancy is highly prevalent in women with asthma.

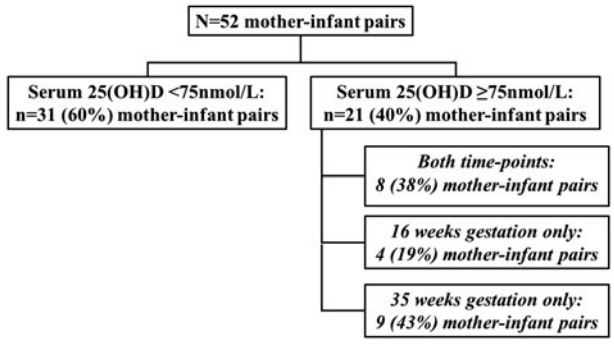

Figure 2. Participant group assignment based on maternal serum 25(OH)D level at an average of 16 and 35 weeks gestation.

pregnancy. Samples were collected at a mean 16.3 (2.7) and 35.4 (2.4) weeks gestation. Across the whole sample, mean serum 25(OH)D levels were 61 (range 26–110) nmol/L at 16 weeks, and 65 (range 32–116) nmol/L at 35 weeks, gestation. Most women had low vitamin D status at both 16 and 35 weeks gestation (Figure 1). In early pregnancy, 29% had 25(OH)D levels <50 nmol/L, 48% between 50–74.9 nmol/L, and 23% ≥ 75 nmol/L. In late gestation, 25% had 25(OH)D levels <50 nmol/L, 42% between 50–74.9 nmol/L, and 33% ≥ 75 nmol/L. Women were grouped according to vitamin D status (Figure 2): 31 (60%) had 25(OH)D < 75 nmol/L at both 16 and 35 weeks gestation, whilst 21 (40%) had 25(OH)D ≥ 75 nmol/L at one or both time-points.

There were no significant group differences in maternal or infant characteristics, when compared by maternal 25(OH)D status during pregnancy (Table 1). Maternal 25(OH)D levels <75 nmol/L during pregnancy were associated with a significantly higher proportion of infants with parent-reported "wheeze ever" at 12 months of age, compared with maternal 25(OH)D ≥ 75 nmol/L (71% [$n = 22$] versus 43% [$n = 9$] $p = .04$). A significant difference was also observed for infant acute-care presentations and OCS use due to parent-reported "wheeze/asthma", in favour of higher maternal 25(OH)D during pregnancy (Figure 3). No significant difference was observed for hospitalisations, ICS or short-acting β-agonist (SABA) use at 12 months of age (Figure 3).

The proportion of infants with ≥four wheezing episodes (40% [$n = 8$] versus 27% [$n = 3$], $p = .48$), ≥four respiratory tract infections (55% [$n = 17$] versus 33% [$n = 7$], $p = .13$), bronchiolitis (43% [$n = 13$] versus 24% [$n = 5$], $p = .15$) or croup (13% [$n = 4$] versus 0%, $p = .14$) did not differ significantly between the group with low, versus high, maternal 25(OH)D during pregnancy.

Discussion

In pregnant women with asthma, we found that 77% in early–mid gestation (16 weeks) and 67% in late gestation (35 weeks) had serum 25(OH)D levels <75 nmol/L. Furthermore, we observed a significant association between persistently low vitamin D status during pregnancy and a higher risk of parent-reported "wheeze" in their infants, as well as clinically important increases in acute-care presentations, hospitalisations, and rescue medication use in the first 12 months of life.

Maternal 25(OH)D levels during pregnancy were <75 nmol/L in most participants; notably, this persisted across pregnancy in 60% of women. This is consistent with literature reporting low 25(OH)D levels are highly prevalent during pregnancy, with average maternal 25(OH)D levels in the western Pacific region at 42–72 nmol/L [1]. A study examining maternal midgestation and cord blood 25(OH)D levels as an indicator of persistent vitamin D deficiency, found one in five mother–infant dyads were severely deficient (defined as 25(OH)D < 25 nmol/L) at both time-points, with another 29% severely deficient at either time-point [19]. Our finding highlights that vitamin D status needs to be addressed in the nutritional care of pregnant women with asthma.

In this sample of pregnant women with asthma, we essentially compared *transiently* versus *persistently* low vitamin D status. Most (62%) women in the high 25(OH)D group had a transient level below/above the

Table 1. Maternal and infant characteristics grouped by maternal vitamin D status during pregnancy.

Variable	Maternal 25(OH)D < 75 nmol/L ($n = 31$)	Maternal 25(OH)D ≥ 75 nmol/L ($n = 21$)
Maternal characteristics		
Age, years	28.1 (5.8)	28.6 (6.8)
Parity, *n*	0 [0, 1]	1 [0, 1]
Ethnicity: Caucasian, *n* (%)	29 (94%)	17 (81%)
RCT group allocation: Intervention, *n* (%)	17 (45%)	11 (48%)
Supplement use during pregnancy, *n* (%)	10 (32%)	7 (33%)
ICS use at baseline, *n* (%)	7 (23%)	7 (33%)
ICS dose, µg	800 [800, 1000]	800 [400, 800]
Exacerbations postrandomisation, *n* (%)	14 (45%)	5 (24%)
Smoking during pregnancy, *n* (%)	3 (10%)	4 (19%)
BMI, kg/m^2	30.5 (7.8)	27.2 (5.2)
BMI category: healthy weight/overweight/obese, %	26/19/55	38/33/29
Gestational weight gain (16–35 weeks), kg[a]	7.3 (4.2)	7.1 (4.1)
Weight gain per week above recommendations, *n* (%)[a]	20 (74%)	13 (68%)
Infant characteristics		
Gestational age at birth, weeks	39.4 (1.5)	39.2 (2.0)
Birth weight, grams	3469.8 (593.0)	3291.6 (586.8)
Gender: Male, *n* (%)	13 (42%)	7 (33%)
Ethnicity: Caucasian, *n* (%)[b]	24 (86%)	13 (65%)
Birth season: Summer/Autumn/Winter/Spring, %	32/16/19/32	33/14/29/24
Breastfed (ever), *n* (%)	26 (84%)	16 (76%)
Breastfed (current at 12 months), *n* (%)[c]	6 (21%)	4 (20%)
Day care attendance, *n* (%)	11 (36%)	5 (24%)
One or more siblings, *n* (%)	15 (48%)	12 (57%)
Siblings, *n*	2 [1, 3]	1 [1, 2]
Smoke exposure: maternal, *n* (%)	3 (10%)[d]	4 (19%)
Smoke exposure: household (exc mother), *n* (%)	6 (20%)[d]	8 (40%)[d]

Data presented as mean (SD), median [IQR], or *n* (%).
[a]$n = 27$ and $n = 19$ had available data in the <75 nmol/L versus ≥75 nmol/L group, respectively.
[b]$n = 28$ and $n = 20$ had available data in the <75 nmol/L versus ≥75 nmol/L group, respectively.
[c]$n = 29$ and $n = 20$ had available data in the <75 nmol/L versus ≥75 nmol/L group, respectively.
[d]$n = 1$ missing data.

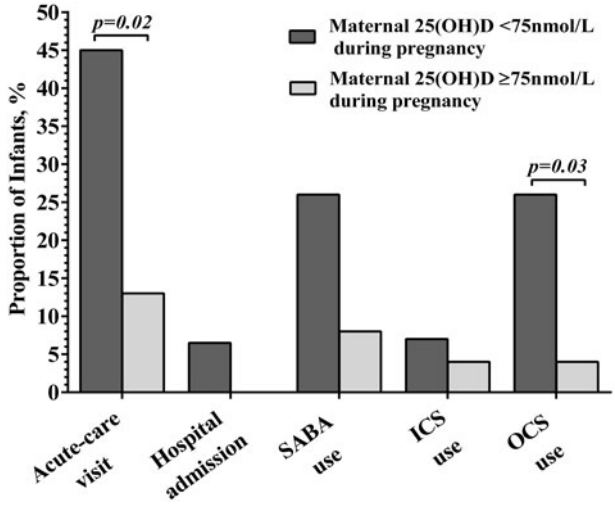

Figure 3. Maternal vitamin D serum 25(OH)D < 75 nmol/L at both 16 and 35 weeks gestation is associated with increased healthcare utilisation and medication use related to adverse infant respiratory outcomes in the first 12 months of life. SABA: short acting β-agonist; ICS: inhaled corticosteroids; OCS: oral corticosteroids.

75 nmol/L cut-point, which highlights two important points. Firstly, our data indicates that a single measurement is not reflective of overall vitamin D status during pregnancy. This is a limitation of many studies, and of meta-analyses which compare respiratory outcomes in studies where a single measurement has been collected, with the heterogeneity in sampling time-point a limiting factor. Secondly, our data highlights that low vitamin D status during pregnancy is a significant nutritional problem in this group: only 15% of women maintained a high vitamin D status from 16 to 35 weeks gestation. Newborn vitamin D levels largely depend upon maternal values [1]; thus, addressing this nutritional deficit in women with asthma during pregnancy is essential to reduce the impact on both maternal and infant health.

This study demonstrated that having 25(OH)D ≥ 75 nmol/L, at just one or two time-points during pregnancy, was associated with less adverse respiratory outcomes in infants at high risk for developing asthma. Specifically, a lower proportion of infant wheeze and associated healthcare utilisation and rescue medication use, which is indicative of more severe episodes of wheeze, during infancy. This is an important finding as wheeze in the first years of life has been implicated in lung function deficits that persist into adulthood and increase the risk of asthma [20,21]; therefore, the potential for maternal nutritional status to influence early life respiratory outcomes in a group

at high risk of developing asthma may represent a promising strategy for primary prevention.

Many epidemiological studies and meta-analyses have reported inverse associations between maternal and cord blood 25(OH)D levels with the risk of infant respiratory infections and preschool wheeze [7,22]; such an association may be modified by the sample type or time-point of collection, with a meta-analysis showing a stronger association for cord blood (versus maternal blood) with risk of infant wheeze [7]. This may suggest that late pregnancy 25(OH)D levels are more relevant to offspring respiratory health; however, due to heterogeneity in the gestational time-points in the included studies, further investigation is warranted [7]. Moreover, recent data from a combined analysis of two RCTs reported that the effect of prenatal vitamin D supplementation on "recurrent wheeze/asthma" at age 3 years was strongest in women who had 25(OH)D levels $\geq$75 nmol/L at randomisation (10–18 weeks and 22- to 26-week gestation, respectively) [23].

A meta-analysis of recent RCTs of vitamin D supplementation during pregnancy revealed high, versus low, vitamin D supplementation was associated with a significantly lower risk of recurrent wheeze in offspring (relative risk 0.81, 95%CI: 0.67–0.98) [24]. Furthermore, *Chawes et al.* found a significant difference in the number of episodes of "troublesome lung symptoms" in the first 3 years of life in infants of mothers who received vitamin D supplements during pregnancy, versus controls (1.3 [0.2–2.4], $p = .02$) [25]. Another clinical trial of maternal vitamin D supplementation during gestation reported the effect size to decrease with infant age, with the maximal group difference in infant wheeze (8.9%) detected at 12 months [26]; this suggests that the effect of maternal vitamin D supplementation during pregnancy on infant respiratory outcomes may be greater in the first 12 months of life. Our results add to the evidence base suggesting vitamin D status during gestation in women with asthma is associated with infant respiratory outcomes in the first 12 months of life, an important determinant of future respiratory health.

Our observation that high maternal vitamin D status during pregnancy is associated with less adverse respiratory outcomes in offspring, could be mediated *via* 25(OH)D exposure *in utero* or during infancy. It may also be that a higher level of serum 25(OH)D is an indicator of overall maternal health and nutritional status, and this may be the important factor in optimising infant outcomes [27]. Alternatively, with evidence to suggest a role for both prenatal and postnatal vitamin D exposure in lung development, it is possible that the observed association is mediated by suboptimal vitamin D status in the infants themselves; unfortunately, we did not measure cord blood or infant 25(OH)D levels. Longitudinal studies with repeat measures of 25(OH)D in both mother and infant are needed to examine the interaction between 25(OH)D level and time-point of exposure from early development.

This study was a secondary analysis of a small sample of pregnant women with asthma, with follow-up of their infants at 12 months of age. Despite a small sample size, we observed a considerable effect size for wheeze and related healthcare utilisation, in high-risk infants. Secondly, we dichotomised high vitamin D status as 25(OH)D $\geq$ 75 nmol/L at one or two time-points; with a larger sample, we may have observed a greater effect size for women who had levels $\geq$75 nmol/L at both time-points. Infant respiratory outcomes were parent-reported and not confirmed through medical records or more objective approaches, and data on sunshine exposure, skin type or infant supplement use were not available. Lastly, although we collected samples at two time-points during pregnancy, we did not have an early trimester measure, nor did we collect a cord blood or infant blood sample, which may represent important time-points in relation to infant respiratory health. Follow-up studies in a much larger cohort are warranted, using more objective outcomes, and repeat measures of maternal and infant 25(OH)D levels.

In summary, low vitamin D status is common in pregnant women with asthma and may influence infant respiratory outcomes and health-care usage in the first 12 months of life. This observation in a group of children who are at high risk of asthma development, warrants further investigation in a larger cohort.

Acknowledgements

The authors acknowledge Kelly Steel and Karen McLaughlin for recruitment and clinical follow-up of the study participants.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This study is supported by National Health Medical Research Centre and Hunter Medical Research Institute.

ORCID

Megan E. Jensen http://orcid.org/0000-0001-8653-4801
V. E. Murphy http://orcid.org/0000-0003-3282-1324

P. G. Gibson http://orcid.org/0000-0001-5865-489X
J. Mattes http://orcid.org/0000-0003-3729-5722
C. A. Camargo Jr. http://orcid.org/0000-0002-5071-7654

References

[1] Saraf R, Morton SM, Camargo CA, Jr., et al. Global summary of maternal and newborn vitamin D status – a systematic review. Matern Child Nutr. 2016;12:647–668.
[2] Kramer CK, Ye C, Swaminathan B, et al. The persistence of maternal vitamin D deficiency and insufficiency during pregnancy and lactation irrespective of season and supplementation. Clin Endocrinol (Oxf). 2016;84:680–686.
[3] Confino-Cohen R, Brufman I, Goldberg A, et al. Vitamin D, asthma prevalence and asthma exacerbations: a large adult population-based study. Allergy. 2014;69:1673–1680.
[4] Finklea JD, Grossmann RE, Tangpricha V. Vitamin D and Chronic Lung Disease: a review of molecular mechanisms and clinical studies. Adv Nutr. 2011;2:244–253.
[5] Aghajafari F, Nagulesapillai T, Ronksley PE, et al. Association between maternal serum 25-hydroxyvitamin D level and pregnancy and neonatal outcomes: systematic review and meta-analysis of observational studies. BMJ. 2013;346:f1169.
[6] Wei SQ, Qi HP, Luo ZC, et al. Maternal vitamin D status and adverse pregnancy outcomes: a systematic review and meta-analysis. J Matern Fetal Neonatal Med. 2013;26:889–899.
[7] Feng H, Xun P, Pike K, et al. In utero exposure to 25-hydroxyvitamin D and risk of childhood asthma, wheeze, and respiratory tract infections: a meta-analysis of birth cohort studies. J Allergy Clin Immunol. 2017;139:1508–1517.
[8] Morales E, Romieu I, Guerra S, et al. Maternal vitamin D status in pregnancy and risk of lower respiratory tract infections, wheezing, and asthma in offspring. Epidemiology. 2012;23:64–71.
[9] Camargo CA, Jr., Ingham T, Wickens K, et al. Cord-blood 25-hydroxyvitamin D levels and risk of respiratory infection, wheezing, and asthma. Pediatrics. 2011;127:e180–e187.
[10] Carroll KN, Gebretsadik T, Griffin MR, et al. Maternal asthma and maternal smoking are associated with increased risk of bronchiolitis during infancy. Pediatrics. 2007;119:1104–1112.
[11] Tse SM, Rifas-Shiman SL, Coull BA, et al. Sex-specific risk factors for childhood wheeze and longitudinal phenotypes of wheeze. J Allergy Clin Immunol. 2016;138:1561–1568.e6.
[12] Castro-Rodriguez JA, Forno E, Rodriguez-Martinez CE, et al. Risk and protective factors for childhood asthma: what is the evidence? J Allergy Clin Immunol Pract. 2016;4:1111–1122.
[13] Litonjua AA, Carey VJ, Burge HA, et al. Parental history and the risk for childhood asthma. Does mother confer more risk than father? Am J Respir Crit Care Med. 1998;158:176–181.
[14] Mattes J, Murphy VE, Powell H, et al. Prenatal origins of bronchiolitis: protective effect of optimised asthma management during pregnancy. Thorax. 2014;69:383–384.
[15] Powell H, Murphy VE, Taylor DR, et al. Management of asthma in pregnancy guided by measurement of fraction of exhaled nitric oxide: a double-blind, randomised controlled trial. Lancet. 2011;378:983–990.
[16] Institute of Medicine, National Research Council Committee to Reexamine IOMPWG. The National Academies Collection: reports funded by National Institutes of Health. In: Rasmussen KM, Yaktine AL, editors. Weight gain during pregnancy: reexamining the guidelines. Washington (DC): National Academies Press (US), National Academy of Sciences; 2009.
[17] Strippoli MP, Silverman M, Michel G, et al. A parent-completed respiratory questionnaire for 1-year-old children: repeatability. Arch Dis Child. 2007;92:861–865.
[18] Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96:1911–1930.
[19] Vinkhuyzen AAE, Eyles DW, Burne TH, et al. Prevalence and predictors of vitamin D deficiency based on maternal mid-gestation and neonatal cord bloods: the Generation R Study. J Steroid Biochem Mol Biol. 2016;164:161–167.
[20] Grad R, Morgan WJ. Long-term outcomes of early-onset wheeze and asthma. J Allergy Clin Immunol. 2012;130:299–307.
[21] Martinez FD, Wright AL, Taussig LM, et al. Asthma and wheezing in the first six years of life. The group health medical associates. N Engl J Med. 1995;332:133–138.
[22] Litonjua AA. Vitamin D deficiency as a risk factor for childhood allergic disease and asthma. Curr Opin Allergy Clin Immunol. 2012;12:179–185.
[23] Wolsk HM, Chawes BL, Litonjua AA, et al. Prenatal vitamin D supplementation reduces risk of asthma/recurrent wheeze in early childhood: a combined analysis of two randomized controlled trials. PLOS one. 2017;12:e0186657.
[24] Vahdaninia M, Mackenzie H, Helps S, et al. Prenatal intake of vitamins and allergic outcomes in the offspring: a systematic review and meta-analysis. J Allergy Clin Immunol Pract. 2017;5:771–778.e5.
[25] Chawes BL, Bønnelykke K, Stokholm J, et al. Effect of vitamin d3 supplementation during pregnancy on risk of persistent wheeze in the offspring: a randomized clinical trial. JAMA. 2016;315:353–361.
[26] Litonjua AA, Carey VJ, Laranjo N, et al. Effect of prenatal supplementation with vitamin D on asthma or recurrent wheezing in offspring by age 3 years: the vdaart randomized clinical trial. JAMA. 2016;315:362–370.
[27] Paxton GA, Teale GR, Nowson CA, et al. Vitamin D and health in pregnancy, infants, children and adolescents in Australia and New Zealand: a position statement. Med J Aust. 2013;198:142–143.