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Associations of Vitamin D Levels and Asthma in Children

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This paper addresses studies from the scientific literature that explored the associations of levels of vitamin D in women during pregnancy and their children with the development and improvement of childhood asthma. Over the past decade the interest in associations between levels of vitamin D and onset of childhood asthma has been on the rise. Because of growing scientific evidence based on epidemiological studies examining the associations between vitamin D levels and onset of childhood asthma, methodology of the previous studies can be roughly divided in three separate concepts to better appreciate the available data: 1) asthma outcomes relative to maternal vitamin D levels during pregnancy; 2) asthma outcomes relative to maternal vitamin D supplementation during pregnancy; 3) asthma outcomes relative to vitamin D levels in children. Studies pertaining to each of the groups are reviewed and critically discussed. **Conclusion** – While current evidence of the association between vitamin D levels and development of childhood asthma is inconsistent, we cannot consider that inadequate levels of vitamin D in pregnancy and in children are causally related to onset of asthma and/or asthma exacerbations. Suggested serum levels of vitamin D of >75 nmol/L should be the goal concentration for optimum physiologic functioning.

Introduction

Over the past decade the interest in associations between levels of vitamin D and onset of childhood asthma has been on the rise (Fig. 1). Because asthma is ranked among top 10 causes of disease burden among children aged 5-14 years worldwide (1), there is a considerable interest in both scientific community and lay public to clarify and define potential risk factors for both onset and exacerbation of asthma in this vulnerable population group.

Studies on animal models have identified that vitamin D affects maturation of alveolar type II cells, proliferation of fibroblasts and synthesis of surfactant (2), which are crucial for maturation of epithelium in the airways, enabling optimal lung function since birth. Similarly, active metabolite, 1,25-dihydroxy vitamin D, has impact on allergic response of T- and B-cells, mast cells and dendritic cells (3), suggesting that modification of vitamin D in serum could help reduce allergies, despite transmission of allergic sensitization patterns across multiple generations (4). For this reason, adverse effects and exposures to low or high levels of vitamin D during the period of lung maturation, i.e. in pregnancy and in early life (5), could at least partially explain the origins of childhood asthma.

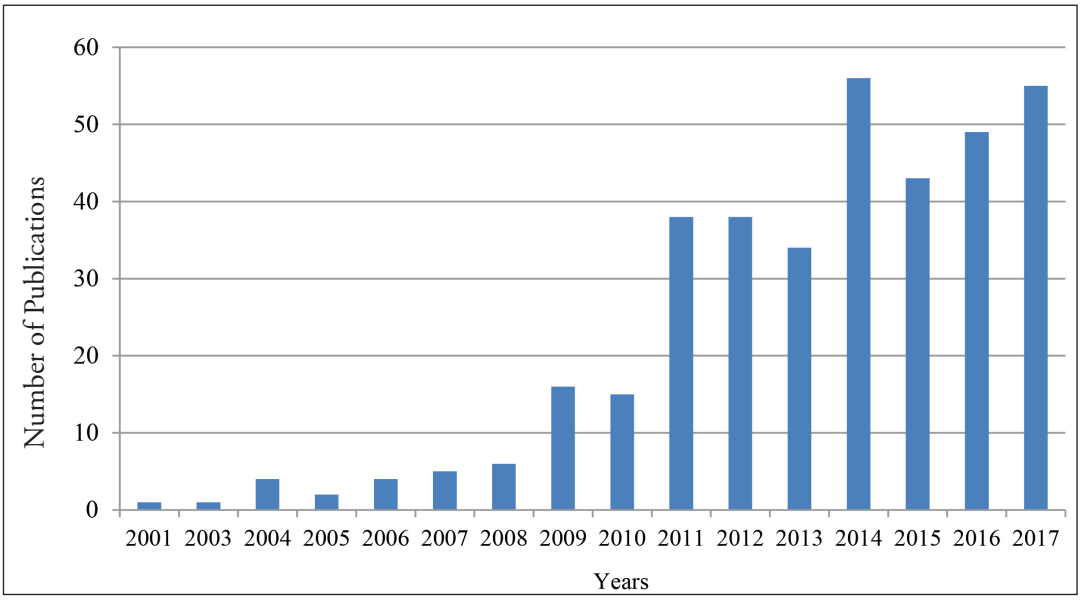

Fig. 1. *Publications on vitamin D, asthma and children on MEDLINE in the period 2001-2017.*

It has been reported that children with asthma who have low vitamin D levels also have low secretion of cathelicidin, a multifunctional polypeptide from macrophages constituting innate immunity (6). In terms of adaptive immunity, it is well-known that immunological response in allergic asthma is mediated by T-helper 17 (Th17) and Th9 cells (7, 8). A study on cell cultures from persons with asthma that were stimulated by dust mite allergen suggested that vitamin D inhibits secretion of IL-9 in Th9 cells as well as downregulates T cell inflammatory response indicating that supplementation of vitamin D could alleviate symptoms of asthma and reduce asthma attacks (8). Also, vitamin D supplementation in second and third trimester of pregnancy was found to promote innate immunity response especially natural killer cells in newborns, which has been linked to reduction in lung diseases including asthma (9). Therefore, the roles of vitamin D in innate and adaptive immune response pathways appears to be of major importance in patho-physiology of asthma.

Because of growing scientific evidence based on epidemiological studies exploring the associations between vitamin D levels and onset of childhood asthma, methodology of the previous studies can be roughly divided in three separate concepts to better appreciate the available data: 1) Asthma outcomes relative to maternal vitamin D levels during pregnancy; 2) Asthma outcomes relative to maternal vitamin D supplementation during pregnancy; and 3) Asthma outcomes relative to vitamin D levels in children.

This paper addresses studies from the scientific literature that explored the associations of levels of vitamin D in women during pregnancy and their children with the development and improvement of childhood asthma.

Asthma Outcomes Relative to Maternal Vitamin D Levels During Pregnancy

In this group of studies, vitamin D levels were examined in two manners. First, maternal vitamin D during pregnancy was assessed through dietary intake. Second, 25-hydroxyvitamin D levels from maternal and cord blood were

measured using liquid chromatography–tandem mass spectrometry, radioimmunoassay, enzyme-linked immunoassay and/or chemiluminescence technologies (10).

Dietary Intake of Vitamin D

This group of longitudinal studies observed the intake of vitamin D through diet and subsequently quantified the levels of maternal vitamin D in pregnancy by means of the Food Frequency Questionnaire (FFQ). The FFQ covers the information on consumption of listed foods and beverages with corresponding quantities during a specific time frame (11).

A large prospective study of nearly 45,000 mother-child pairs from Denmark (12) assessed maternal dietary intake of vitamin D in the second pregnancy trimester. Asthma outcomes were self-reported at age of 18 months and 7 years, and were also cross-checked in national registries. Adjusted regression analysis showed no associations between levels of maternal vitamin D in pregnancy and asthma at age 18 months (12). However, at age 7 years, the authors observed that children of mothers who were in the lowest vitamin D quintile group in pregnancy were at risk of developing asthma compared to children of mothers in the highest vitamin D quintile group (12). A study of 1,924 British mother-child pairs (13) suggested similar results to that of the Danish birth cohort (12) i.e. that higher intake of vitamin D through diet reduces the odds of having asthma in the first 10 years of life. A recent study from Irish cohort of mother-child dyads reported that higher intake of vitamin D in pregnancy, derived from intake of oily fish and vegetables, decreased chances of developing asthma at age 10 years (14). Nevertheless, a meta-analysis including 4 studies exploring the association of maternal nutrition as measured by the FFQs with asthma outcomes in children suggested that maternal higher intake of vitamin D through diet decreases the chance of developing wheezing, but not asthma in their offspring (15).

Although some evidence of protective effect of higher levels of vitamin D on asthma has been reported in this group of studies (12-14), measurement of maternal vitamin D levels in pregnancy by means of FFQs, indeed, has a major drawback, because the calculation of vitamin D intake is mere approximation and not precisely quantified serum level. It has been debated how accurate baseline assessment of nutrients is using the FFQ (16), since it is based on recollection. Self-reported exposures can also be subject to misclassification that could affect estimates of exposure effect. Given that exposure to sunlight and synthesis in the skin represents the main source of vitamin D for humans (17), time spent outside should be taken into consideration when analyzing this particular association, as well as lifestyle and ethicnicity/skin type.

Maternal and Cord Blood Measurement of Vitamin D

Studies measuring levels of 25-dihydroxy vitamin D in maternal serum during pregnancy and its association with childhood asthma reported inconsistent results. A study in Western Australia among 2,834 women documented that lower levels of 25-dihydroxy vitamin D were associated with development of asthma at age 6 years among boys, but not among girls (18). Positive associations between levels of 25-dihydroxy vitamin D and forced volume vital capacity (FVC) and Forced Expiratory Volume in 1 Second (FEV1) at age 6 years and lack of this association at age 14 years suggested that lower levels of vitamin D could be more important over the course of lung development rather than in later childhood (18). Conversely, a study among almost 600 pregnant women from the United King-

dom reported that children of mothers who had serum levels of 25-dihydroxy vitamin D of >75 nmol/L were more likely to develop asthma at 9 years of age (19).

On the other hand, several studies conducted in European populations did not observe associations between lower or higher levels of vitamin D in pregnancy and childhood asthma (16-18). A British study conducted in South West of England (20) followed more than 3,000 mother-child pairs for 7 years with aim at assessing asthma and allergy-related health outcomes. The authors found null association between maternal vitamin D levels in pregnancy and asthma among children aged 7 and 8 years (20). Similarly, a study of 3,130 Dutch mothers and their children reported no associations between lower vitamin D levels and higher airway resistance or fractional exhaled nitric oxide (21). Morales et al. (22) followed 1,724 mother-child dyads in Spain and did not find report higher likelihood of wheezing at age 1 year or 4 years or asthma at age 4-6 years among mothers with lower 25-dihydroxy vitamin D levels in pregnancy.

Optimal 25-hydroxyvitamin D level during pregnancy remains unclear. Thus, widely used cut-offs, such as >75 nmol/L has been used to characterize optimal 25-hydroxyvitamin D levels in pregnancy (23). It has been suggested that pregnant women are particularly prone to vitamin D deficiency (24). This may subsequently lead to inadequate 25-hydroxyvitamin D levels in their newborns. For this reason, several prospective cohort studies have examined the associations between 25-hydroxyvitamin D levels in cord blood and asthma-related outcomes (25-27). A small-scale study of 219 participants from Arizona, United States, reported that low as well as high levels of 25-hydroxyvitamin D in cord blood were associated with higher sensitization to aeroallergen at age 5 years (25). Other studies with similar number of participants (26, 27) did not observe associations cord blood 25-hydroxyvitamin D levels with asthma at age 5 years. However, the set of 3,130 mother-child pairs in a Dutch study found that children of mothers who were in the lowest tertile group of 25-dihydroxy vitamin D level were more likely to have higher airway resistance at age 6 years compared to mothers in the highest tertile group (21). Nevertheless, when multiple model was adjusted for additional variable - current serum level of 25-dihydroxy vitamin D at age 6 years - the observed association was lost (21).

To increase statistical power and sample size, Song et al. (28) conducted a meta-analysis of prospective cohort studies on asthma outcomes in children that included measurements of serum 25-dihydroxy vitamin D levels in pregnancy and/or cord blood. This analysis combined a total of fifteen studies with 12,758 participants and 1,795 children with asthma (28). The authors analyzed 25-dihydroxy vitamin D levels according to cut-off categories as well as continuous values. Pooled relative risk of categorical (0.87) and continuous 25-dihydroxy vitamin D levels (0.99) did not reach the level of statistical significance (95% confidence intervals [CI], 0.75-1.02 and 0.95-1.02, respectively). However, the authors suggested that, when taking into consideration dose-response effect, the levels of 25-dihydroxy vitamin D exhibit U-shape relationship with asthma occurrence in childhood. This means that optimal levels of 25-dihydroxy vitamin D in pregnancy and/or cord blood, such as the range between 70 and 130 nmol/L, could be associated with the lowest risk of asthma onset (28). These findings also suggest that lower and higher levels of 25-dihydroxy vitamin D in pregnancy and/or cord blood than the above mentioned range could potentially be detrimental for early lung functioning (28). Additionally, another meta-analysis of 8 birth cohorts (29), that included both pregnancy

and cord blood measurements of 25-dihydroxy vitamin D levels, suggested similar findings as previously described (28).

Despite inconsistent evidence of the association of vitamin D levels in pregnancy and at birth with childhood asthma, the majority of studies included European, Caucasian population. Although countries with more heterogeneous populations could have included ethnicity in their analyses, it remains unclear whether this could have a major effect on study results in terms of under- and overestimation of the effect vitamin D levels on onset of childhood asthma. Therefore, it is warranted to conduct similar studies in non-Caucasian populations. Also, above mentioned studies were heterogeneous in terms of number of covariates included in the regression models. For this reason, inclusion of few covariates could have overestimated, while inclusion of larger number of covariates could have underestimated the effect of vitamin D levels on childhood asthma. Asthma outcomes have been assessed using different methodologies, such as being parent-reported, doctor-diagnosed or parameters of lung functions were used as asthma proxies. This heterogeneity in measurement could render inconsistencies when measuring the vitamin D effect estimates. Finally, merging of both pregnancy and cord blood levels in a single meta-analysis could have been a methodological issue, given that it is still unclear whether or not 25-dihydroxy vitamin D and other vitamin D metabolites cross the placental blood barrier and to what extent placenta regulates vitamin D secretion and circulation (30).

Asthma Outcomes Relative to Maternal Vitamin D Supplementation During Pregnancy

Further interest in the exposure to the low/high vitamin D levels and its effect on onset of childhood asthma paved the way to several randomized controlled trials where standard recommended vitamin D dosages were compared to additional vitamin D supplementation of the pregnant women (31-35). Women and their offspring were followed for several years, after which respiratory outcomes were examined.

One of the first trials was carried out in the United Kingdom on a sample of 180 pregnant women who were randomized to three groups, whereby first group did not receive any vitamin D, second group received 800 international units (IU) of vitamin D_2 per day from gestational week 27 up to delivery, and third group received a single dose of 200,000 IU of vitamin D_3 orally (31). Children were assessed for respiratory health 3 years after birth and no association was found between supplementation of vitamin D and lower likelihood of wheezing (31). Similarly, a larger double-blind randomized controlled trial including more than 800 women from the United States whose children were at risk of developing asthma due to family history, showed that 3-year old children of mothers who received additional 4,000 IU of vitamin D_3 to standard recommended 400 IU from gestational weeks 10-18 until birth, did have lower rate of incident asthma and recurrent wheezing compared to mothers in the control group who received only 400 IU (32). However, this was not statistically significant (32). A similar protocol of receiving 2,400 IU of vitamin D supplement in experimental group of pregnant women from a double-blind randomized controlled trial in Denmark (33) confirmed the results from the United States (32), suggesting no association between vitamin D supplementation during pregnancy and decreased risk of persistent wheezing at age 3 years.

Nevertheless, when pregnant women from the United States were classified according to baseline levels of serum vitamin D before enrollment in the trial (34), it was observed that

children of mothers who had levels of ≥95 nmol/L (30 ng/L) had significantly lower (almost double) chances of developing asthma/recurrent wheezing compared to children of mothers whose vitamin D levels were <95 nmol/L (30 ng/L) at that point in time. Similar results were obtained when data of the participants in the United States trial and Danish trial were merged and analyzed according to levels of vitamin D at enrollment (35). These findings highlight the importance of adequate vitamin D levels in pregnancy, well-above the suggested optimal 75 nmol/L cut-off (17), relative to offspring lung health.

While results from previous trials assessing the effect of vitamin D supplementation on asthma outcomes in offspring, it should be kept in mind that women who were enrolled conceived children with a partner who had history of asthma, eczema or allergic rhinitis (32). Therefore, the children were at risk of having asthma since birth. While the trial in the United States has included 3 clinical centers (32), the trial from Denmark included pregnant women from a single center (33) and did not elaborate on potential ethnic disparities that could have affected the exposure to vitamin D due to lifestyle and/or diet.

Asthma Outcomes Relative to Vitamin D Levels in Children

The effects of vitamin D have been examined in children affected with asthma. Specifically, several studies were focused on measuring the effect of increased vitamin D in children who have doctor-diagnosed asthma and whether the increase in serum levels could reduce asthma symptoms and/or prevent exacerbations.

A prospective study from the United States that included 1,041 children aged 5 to 12 years with mild to moderate persistent asthma classified the study participants based on their baseline serum levels of vitamin D to sufficient, insufficient and deficient group (36). This study did not involve administration of vitamin D supplement, but rather followed the effect of corticosteroid therapy relative to the levels of vitamin D in children at baseline. After one-year follow-up period, the authors observed that children who were vitamin D deficient had lower lung function compared to those who were vitamin D sufficient (36). This finding suggested that higher vitamin D levels could improve the effects of therapy.

A small-scale randomized controlled trial with 39 children with mild asthma (37) administered a 6-week protocol with 14,000 IU of vitamin D once a week to the experimental group, while the control group received placebo. However, in spite of measurable increase in serum vitamin D levels, children who received the supplement did not differ in terms of improved lung function compared to placebo group (37). Similarly, in a trial including 44 children with asthma, daily dose of 2,000 IU of vitamin D was administered to the experimental group (38). After completing the protocol in 15 weeks, there were no differences between the experimental and control group, even though the only appreciable difference was that the children receiving the supplement had significantly less missed days at school (38).

Finally, the results of two meta-analyses were inconclusive, given that studies on supplementation of vitamin D in children had small study populations (35, 36). Still, their results suggested that supplementation of vitamin D likely prevents asthma exacerbations in children (39), but also that actual advantageous effects of vitamin D on childhood asthma are neither confirmed nor excluded (40).

Conclusion

A complex interplay between vitamin D level and the immune system as well as the allergic response needs to be acknowledged. Robust multi-center randomized controlled trials are required to substantiate whether or not supplementation of vitamin D in pregnancy

and in children affected with asthma can be generalized to the entire worldwide population. While current evidence of an association between vitamin D levels and development of childhood asthma is inconsistent, we cannot consider that inadequate levels of vitamin D in pregnancy and in children are causally related to onset of asthma and/or asthma exacerbations. Suggested serum levels of vitamin D of >75 nmol/L should be the goal concentration for optimum physiologic functioning.

Conflict of interest: The author declares that she has no conflict of interest.

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