Narrative Review:
Maternal Vitamin D Status and Children's Asthma or Wheezing: A Narrative Review

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ABSTRACT

Context: Asthma is a chronic inflammatory respiratory disorder, and nutritional conditions affect allergic diseases such as asthma. This study aims to find the relationship between maternal gestational vitamin D levels and asthma progression and wheezing in children later in life.

Objectives: Allergic disorders are common everywhere in the world. Asthma is the most chronic inflammatory respiratory disorder among children. It causes significant morbidity and mortality in children as well as adults. Vitamin D deficiency or insufficiency, is a global problem. Vitamin D has immunological effects, and it may prevent autoimmune diseases. Maternal plasma vitamin D during pregnancy has a different impact on children's allergic disorders.

Evidence Acquisition: This is a review article. We searched databases, including Google Scholar, PubMed, SID, IranDoc, Scopus, until now. The keywords for the search included Maternal vitamin D, Asthma, Wheezing, Children, and Pediatric. We searched in the mentioned databases until March 2020. Full-text articles in the English language were included in this study.

Results: A few articles were found in our search. All of them were cohort studies. They evaluated maternal vitamin D and its outcomes in their children's asthma and wheezing using questionnaire data and serum samples. After assessing the articles (more than 100), 15 papers were included in our review. Six and four articles showed that higher maternal vitamin D levels reduce children's asthma and or wheezing, respectively. In contrast, 7 articles showed no association between maternal vitamin D and children's asthma or wheezing. Vitamin D does not have any serious side effects. Because the articles were heterogenic, a meta-analysis could not be done.

Conclusions: Administering vitamin D supplements or food enriched vitamin D during pregnancy has different effects on the prevalence of wheezing and or asthma in children.

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1. Context

Allergic disorders are common all over the world. Asthma is the most chronic inflammatory respiratory disorder among children. Asthma causes significant morbidity and mortality in children as well as adults. Asthma is the most common cause of emergency department visits, absence from school, and children's hospitalization. Common clinical manifestations of asthma are cough, wheezing, and dyspnea. The prevalence of asthma differs from one region to another (1, 2). Globally more than 300 million people have been affected. Asthma is more common in children than adults (1-3). The prevalence of asthma is increasing in the past several decades, probably due to environmental and or genetic susceptibilities, as well as economic and nutritional factors (4, 5). Asthma has a high burden on families and healthcare systems (6). Although the etiology of asthma is not precisely clear, genetic and environmental factors have an essential role in inducing and exacerbating asthma.

Different cytokines and chemokines, such as interleukin (IL)-6 and IL-8, contribute to the pathogenesis of asthma (7-9). Diagnosis of asthma is mainly dependent on the patient's history and physical examination. Treatments of asthma include avoiding risk factors such as indoor and outdoor allergens, pharmacotherapy for alleviative and conservative treatments, and in some instances, specific allergen immunotherapy (1). Knowledge of etiology and or triggers helps us to control asthma better. Trace elements and vitamins may contribute to the pathogenesis of asthma. It has been hypothesized that a recent change in diet may contribute to increased asthma. Vitamin D has nutritional and hormonal properties. Vitamin D has immunological effects, and it may prevent autoimmune diseases. Maternal plasma vitamin D during pregnancy has a different impact on children's allergic disorders. Vitamin D induced statement of CD23/21 (low-affinity IgE receptor on B cells) and FoxP3 (forkhead box P3) factor might be influential on the severity and remodeling of asthma (7, 10-12).

The immunomodulatory effects of vitamin D protect against allergic diseases. Most studies support that vitamin D has protective effects against asthma (its severity and pulmonary function) and wheezing (13-15). However, a few articles found no relationship between vitamin D levels and asthma (16, 17). Vitamin D supplements were very effective in improving the clinical status of asthma in children with vitamin D insufficiency (18).

Nutrition is a minor source of vitamin D. Skin when exposed to sunshine is the primary source of vitamin D. Vitamin D deficiency or insufficiency is a global problem. Risk factors for vitamin D deficiency include 1. Low ambient ultraviolet radiation: northern latitudes, winter season, high level of air pollution, 2. Limited sun exposure: excessive sun avoidance (i.e. shade, sunscreen), extensive clothing cover, staying indoors, 3. Host factors: dark skin, obesity, aging, inappropriately low dietary intake, malabsorptive syndrome (i.e. celiac disease, Whipple's disease, cystic fibrosis, imitator bowel syndrome, short gut syndrome), liver and renal diseases, use of certain drugs (i.e. glucocorticoids, phenytoin, phenobarbital, highly active antiretroviral therapy, rifampin) (18, 19). Maternal vitamin D has variable effects on children's asthma and recurrent wheezing. Some articles confirmed that administrating vitamin D during pregnancy decreased allergic disorders such as asthma and wheezing in their children, but others did not show significant effects (19). This study aims to review maternal vitamin D and the prevalence of children's asthma and or wheezing.

2. Evidence Acquisition

This study is a narrative review article about the association of maternal vitamin D use during pregnancy with asthma and whizzing in their children by searching in international electronic databases of Google Scholar, PubMed, Scopus, until now and Iranian databases of SID and IranDoc up to one month ago. All of the authors contributed to the search study. The keywords for our search included "Maternal vitamin D", "Children's asthma", "Children wheezing", "Pediatric asthma", "Pediatric wheezing", and "Allergy disease". There were no time limitations for the search. All full-text articles in the English language were included in this study. The inclusion criteria for the articles are evaluating vitamin D status during pregnancy, such as serum vitamin D, vitamin D supplement and vitamin D from nutrition, prospective or retrospective study, with or without control, and with any sample size.

3. Results

We found more than 100 articles in this area. After their evaluation, 15 articles were included in our review. All of those studies are cohort type. Six and four articles reported that higher maternal vitamin D levels would reduce children's asthma and or wheezing, respectively. In contrast, 7 and 7 articles showed no association between maternal vitamin D and children's asthma or wheezing, respectively. Two and four articles did not evaluate the association between maternal vitamin D and children's asthma or recurrent wheezing, respectively (Tables 1 and 2).

Table 1. Maternal vitamin D characteristics and children's outcomes of asthma/wheezing

Authors	Maternal Case No.	Median Plasma Vitamin D Level in Pregnancy or Intake of Vitamin D	Age Evaluation of The Children/No.	Total of Children Studied/ Percentage of Asthma Prevalence	Total of Children Studied/ Percentage of Wheezing Prevalence	Kind of Evaluation and Study
Morales et al. (20)	2502	29.5 ng/mL, <12 weeks of pregnancy	At 1 year At 4-6 year	1233/20	1724/30 1233/18	Questionnaires Cohort
Erkola et al. (19)	1825	260 IU±152 IU/d vitamin D intake	5 years	1669/6	1669/15	Questionnaires Cohort
Gale et al. (11)	596	20 ng/mL serum level, <17 weeks of pregnancy	9 months 9 years	440 178/11		Questionnaires Cohort
Pike et al. (21)	860	23.6 ng/mL serum level, 34 weeks of pregnancy	6 years 6 years	860/10	860/16	Questionnaires Cohort
Deveruex et al. (22)	1751	128 IU/d[a], 32 weeks of pregnancy	2 years 5 years	1374 1212	1374/7.6 1212/7.6	Questionnaires Cohort
Deveruex et al. (23)	1924	144 IU/d[a] , vitamin D intake	15 years	747/15	747/33	Questionnaires Cohort
Maslova et al. (24)	44825	468 IU/d[a], <10 weeks of pregnancy	18 months 7 years	33425/17 28687/4	-	Questionnaires Cohort
Camargo et al. (25)	1306	548±167 IU/d, vitamin D intake	3 years	1194/11	1194/7	Questionnaires Cohort
Allan et al. (26)	1924	144 IU/d[a]	10 years	1748/16.8	1748/36	Questionnaires Serum test
Zosky et al. (27)	929	>30 ng/mL serum level, 16-20 weeks	6 years 14 years	291/0.12* 288/0.16*	291/0.03* 288/0.47*	Questionnaires Serum test
Chiu et al. (28)	164	23.2±7.7 ng/mL, serum level	4 years	182/16	-	Questionnaires Serum test
Goldring et al. (29)	180	800 IU ergocalciferol or a single oral dose of 200000 IU cholecalciferol[a], 27 weeks	3 years	-	108/16	Telephone Cord blood test Cohort
Anderson et al. (30)	2443	⩾20 ng/mL serum level	0-5 years	1275/6	1275/20	Questionnaires Cohort
Lintonjua et al. (31)	881	4400 IU/d[a] , 10-18 weeks of pregnancy	6 years	360/55	360/95.6	Questionnaires Blood test

*P; [a]Daily vitamin D intake.

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4. Discussion

Vitamin D is an essential vitamin in the body that plays many roles in the fetus and children's physical growth, including their respiratory systems (32). Vitamin D has different effects on atopy and allergic disorders. The exact amount of daily intake of vitamin D in a pregnant woman to reduce allergic diseases in children is unknown (33). We found articles that have variable validations due to different sample sizes, not assessing vitamin D in all mothers and children, different follow-up durations of children, varying doses of vitamin D administration in mothers, different gestation age of vitamin D administration, ambiguity about excluding or including concurrency factors and so on. In our review, more studies had low validity because they used questionnaires for collecting information (13, 22-25, 29), but some had higher quality because they evaluated plasma vitamin D levels in mothers (20, 21, 27). As regards, research studies had different sample sizes, variable vitamin D supplement, and dietary, different children's ages follow-ups, their results were different (Tables 1 and 2).

Zosky et al. believed that there was an association between vitamin D during pregnancy and children's lung function but not with fetal and post-natal somatic growth. Girls are more susceptible to maternal vitamin D levels during fetal lung development (27). Multiple factors contribute to fetus lung maturation, including androgens, estrogen, surfactant (27). Impaired lung function in early life is strongly associated with chronic lung disorders in adulthood (34).

Some studies of this review revealed that higher intake of vitamin D by dietary or supplement during pregnancy was associated with a reduction in children's asthma (13, 23-27, 28, 30) and wheezing (22, 23, 25, 26). All of the studies except one reported that maternal vitamin D would decrease asthma (associate group) in their children evaluate intake of vitamin D (from 144 to 548 IU/d) (13, 23-26), only one study (without control group) by evaluated serum vitamin D in mothers (23 ng/mL) (28). Instead, all of the studies except one reported that maternal vitamin D did not decrease children's asthma (no control group) by evaluate serum vitamin D (20 to more

Table 2. The relationship between maternal vitamin D level and children's asthma or wheezing

Author	Asthma in Children	Wheezing in Children	Other Disorders in Children
Erkola et al. (19)	Significantly decreased	NA	
Gale et al. (11)	Significantly increased when maternal serum Vit D >30 ng/mL	NA	Eczema significantly increased when maternal serum Vit D >30 ng/mL
Wjst et al. (12)	NS	NA	-
Morales et al. (20)	NS	NS	-
Pike et al. (21)	NS	NS	-
Deveruex et al. (22)	NA	Significantly decreased	-
Deveruex et al. (23)	Significant decreased	Significantly decreased	-
Maslova et al. (24)	S* NS at 18 months	NS	-
Carmago et al. (25)	Significantly decreased	Significantly decreased	-
Allan et al. (26)	Significantly decreased	Significantly decreased	-
Zosky et al. (27)	NS at 14 years both genders NS at 6 years in girls	NS at 14 years in both gender	Decreased in FVC at 6 years with low maternal vitamin D. No change in FEV1 at 6 years, FVC at 14 years and FEV1 at 14 years
Chiu et al. (28)	Significantly decreased	NA	Decreased eczema at 4 years
Goldring et al. (29)	NA	NS	No change in AR, food allergy, eczema, and LRTI
Anderson et al. (30)	NS	NS	-
Litonjua et al. (31)	NS	NS	No change in eczema, AR, LRTI, PFT

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NS: Not Significant; NA: No Assessment; S*: At the age of 7 years; AR: Allergic rhinitis; LRTI: Lower Respiratory Tract Infection; PFT: Pulmonary Function Test; FVC: Forced Vital Capacity; FEV1: Forced Expiratory Volume in 1 second

than 30 ng/ml) (16-18, 27, 30), only one study assessed the maternal intake of vitamin D (4400 IU/d) (31). Therefore, we cannot compare the two groups because they used different methods for evaluations.

Also, about wheezing, all of the studies reported that maternal vitamin D decrease children's wheezing (associate group) evaluate maternal intake of vitamin D (128-548 IU/d) (22, 23, 25, 26), instead of in another group (no associate group) all of them except two studies evaluate serum maternal vitamin D (from 20 to 30 ng/mL) (20, 21, 27, 30) and two studies assessed the maternal intake of vitamin D (4684400 IU/d) (24, 31). Associated group could not be compared with associated group because it is different from their evaluation ways. Higher vitamin D intake during pregnancy causes reduced asthma and wheezing in children up to 7 years old (24). They believed that low vitamin D intake during pregnancy was related to reduced lung functions in fetuses, and children with increasing wheezing and asthma (24).

Surfactant deficiency and alteration of the immune system due to vitamin D deficiency could be another contributing factor. Alteration of the immune system in maternal vitamin D intake decreases pro-inflammatory cytokine Interleukin-3 (IL-3) release and increases the anti-inflammatory cytokine IL-10 (35). Vitamin D also controls the proliferation and hypertrophy of smooth muscles (36, 37). Other vitamins and micronutrients may be contributed to the development of the fetus respiratory system. In one study, vitamin E, zinc, and selenium levels were higher in mothers with higher vitamin D levels, but they did not affect the asthma prevalence in children; however, in this study, vitamin D alone effectively reduced asthma in children (13). Yet, in another study, a combination of vitamins D and E was associated with decreased asthma and wheezing in children up to 10 years old but not in 15-year-old children (23). Another study showed that a variety of micronutrients (e.g. vitamin C, vitamin E, and zinc) did not have more effects than the results of maternal vitamin D on the asthma of children up to 3 years old (25).

A study showed higher maternal vitamin D decreased asthma and wheezing in children up to 4 years old. Still, allergy sensitization increased in children less than 2 years of mothers with lower vitamin D (28). Allan et al. found a decrease in asthma and wheezing of children whose mothers had a higher vitamin D during pregnancy (26). Lower maternal vitamin D was associated with reduced Forced Expiratory Volume at 1 second (FEV1) of children up to 5 years old (22). Consuming vitamins or micronutrients during pregnancy has different effects on children's asthma and wheezing (no effects on decrease).

Contrary to previous articles, some articles reported that the maternal intake of vitamin D was associated with increased cases of allergic diseases such as asthma (five times) at 9 years and eczema at 9 months in their children (11) and atopy or atopic disorders in children (12). A small sample size of 9-year-old children is a limitation of this study. The study has a low-quality value because the diagnosis of eczema and asthma was based on questionnaires. They believed that vitamin D was associated with the proliferation of the allergy-inducing T helper type 2 cells based on Matheu's study in mice (10-12).

Researchers also evaluated other disorders such as eczema, lower tract infections, allergic rhinitis, and bronchitis, along with asthma and or wheezing. They reported a decrease in eczema in children up to 4 years old (28), lower tract infections (20), and allergic rhinitis (13) in 5-year-old children whose mothers had higher serum vitamin D. There are no association between maternal vitamin D and bronchitis or respiratory infections (11, 25, 29, 31), food allergy (29), allergic rhinitis (24, 29, 31), eczema (13, 22, 25, 29, 31) or atopy and atopic sensitization (21, 22, 27-29), fractional exhaled nitric oxide (22) and lower tract infections (11, 25, 31) in children.

Other researchers reported no significant association between maternal vitamin D and children's asthma (16-21, 27) and wheezing (20, 21, 24, 27, 29). The ages of following for wheezing were 1 and 4 years, for current asthma was 4-6 years (20); 18 monthly for asthma and 9 monthly for wheezing (24). There was no association between maternal vitamin D and asthma and wheezing in children up to 14 years old and asthma in girls up to 6 years old (27).

Some reasons for different results in our articles are related to their different sample sizes, duration of follow-ups in children from 6 months (10) to 15 years (23), maternal dietary and supplement of vitamin D, and way of assessments. Often researchers followed children for 3-7 years (19-22, 24, 25, 28). We found in a study that two-thirds of asthma or recurrent wheezing in children improved before their teen years (38). It indicates how vitamin D can affect prevention or reduction of persistent childhood asthma after 10 years. We need more study for a longer duration following children. Intake of vitamin D by dietary or supplement in our reviewed articles was variable, from 3.6 µg/d (20) to 11.7 µg/d (24). This variation can affect the outcome of children's asthma and wheezing. Low or higher criteria for serum maternal vitamin D level were different between studies from 59 nmol/L (21) to 75 nmol/L (27). Because there is no standard criterion for serum level of maternal vitamin D, the results of studies are different. The amount of vitamin D intake by food or supplement could not meet the right criteria reported in some articles (19, 23, 26). Timing of vitamin D supplementation or serum level of vitamin D might be important. In our search, we found different timing evaluations of serum maternal vitamin D or intake of vitamin D amount by questionnaires, for example, from 10 weeks pregnancy (24) to 34 weeks of pregnancy (21). The immune system, including B and T cells, is differentiated before 4 weeks of pregnancy in a fetus then progresses later; therefore, optimal vitamin D intake must be evaluated in this regard. In a study, the researchers found that preterm delivery, male sex, maternal overweight/obesity, and maternal smoking during pregnancy were more common among children diagnosed with asthma at the age of 4-6 years (20).

5. Conclusions

Vitamin D supplements or food during pregnancy has different effects on the prevalence of wheezing or asthma in children. We need more prospective cohort and or clinical trial studies for maternal vitamin D effects on children's allergic disorders such as asthma or wheezing.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles are considered in this article. The participants were informed of the purpose of the research and its implementation stages.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflicts of interest

The authors declared no conflict of interest.

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