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Abstract:
Vitamin D is important in growth and development as well as immunity. Recently, research has shown that vitamin D can also play a significant role during pregnancy and affect infant and childhood outcomes. Based on a review of seven studies, dietary vitamin D during pregnancy may decrease the risk for low birthweight and childhood asthma in progeny. In regards to infant birthweight, increasing levels of dietary vitamin D intake during pregnancy is associated with higher birthweights. In addition, studies show that progeny of mothers with a higher dietary intake of vitamin D during pregnancy have a lower risk for asthma and wheezing symptoms. However, the lack of serum data and randomized controlled trials suggest the need for further research to validate these findings.

INTRODUCTION

Vitamin D is most widely recognized in its role in calcium absorption and bone growth; nonetheless it also plays a role in the regulation of immunity (1). There has been conflicting accounts of whether Americans meet the recommended intake for Vitamin D. From an earlier report of vitamin D intake, only 50% of Americans met the recommended intake for vitamin D (2). The most recent report from the National Academy of Sciences has concluded that the majority of Americans and Canadians are probably getting enough vitamin D and calcium to meet their needs, although the report also noted a lack of consistency in relationship to cut points defining adequate intake (3). Vitamin D deficiency in certain sub-populations nonetheless, may greatly influence adverse health outcomes (4). Multiple studies indicate that vitamin D deficiency is especially significant during pregnancy, as it has been linked to increased rates of caesarean section, gestational diabetes, and preeclampsia (5-7). Further, vitamin D deficiency affects the fetus relative to its dependence on maternal consumption, absorption, and metabolism of dietary sources (5,6).

Experts suggest newborn hypocalcemia, impaired growth, low bone mineral density, skeletal deformities, small size, and seizures are associated with low vitamin D during pregnancy (5). Of particular concern is low birthweight (LBW), as disorders related to short gestation and LBW are the second leading cause of infant mortality (8). As >300,000 LBW infants are born annually in the US (9), the total annual cost of health care may exceed $5.8 billion (10). Given the negative impact of LBW, some propose 25-hydroxyvitamin D (25 OHD) concentrations of 32-80 ng/mL in serum will optimize maternal and fetal health during pregnancy (7). Yet, data from early randomized controlled trials (RCTs) are conflicting (10, 11). For example, while Marya et al. found maternal serum vitamin D showed influences risk for LBW (11), Mallet et al. showed no effect (12). More recent studies may support the use of vitamin D supplementation during pregnancy to prevent LBW.

Additionally, recent data further suggest that LBW and pregnancy-related vitamin D are both independent risk factors for childhood asthma (13-15). Asthma currently affects >7 million children in the US and is the leading cause of childhood hospitalizations, emergency room visits, and disability (16, 17). Recent evidence suggests asthma may develop *in utero,* causing some to focus on the influence of maternal diet, including maternal dietary vitamin D (18, 19). Thus, this review will explore the link between maternal dietary vitamin D with LBW and asthma.

METHODS

To identify evidence for the protective effect of maternal dietary vitamin D against LBW and asthma in progeny, PubMed was searched with combinations of the following key words: "dietary vitamin D", "maternal vitamin D", "vitamin D intake", "supplementation", "maternal diet", "vitamin D deficiency", "hypovitaminosis D", "pregnancy", "prevention", "low birth weight", "childhood asthma", "wheeze", and "allergy." A total of 916 articles were identified. Search results were then limited to English and all children 0-18 years old. Articles reviewed included cross-sectional studies, cohort studies, and randomized controlled trials. Epidemiologic studies were selected if the exposure of interest was dietary maternal vitamin D and the outcome of interest was LBW, birthweight, asthma, or asthma-related symptoms in infants and children. For more recent perspectives, articles published prior to 2006 were excluded from this review. From these criteria, seven peer-reviewed data-based studies were identified for this review.

RESULTS

Three epidemiological studies examined the relationship between maternal dietary vitamin D and infant birthweight. In cross-sectional data, 449 healthy pregnant women and their newborns were enrolled from three university hospitals in Iran (20). Dietary vitamin D during pregnancy were obtained using a food-frequency questionnaire and weight, length, and head circumference were measured for each newborn. Among newborns whose mothers consumed at least 5 μg/day of calcium and vitamin D, the incidence of LBW was lower ($p = 0.007$) (20) (Table 1).

A cohort of 504 pregnant New Zealand clinic attendees found a positive association between vitamin D intake and birthweight (21). Follow-up at 4-7 months of pregnancy assessed 24-hour and 3-day food recall for vitamin D; infant birthweight was obtained from medical records. After controlling for maternal height, weight, number of adults and preschoolers in the household, smoking status, and infant gestational age and sex, maternal dietary vitamin D at 4 months was associated with an increase in birthweight of 71 g ($p = 0.015$) (21) (Table 1).

Another prospective study of 2,251 minority female urbanites showed low vitamin D consumption was associated with lower birthweight (22). Average daily maternal consumption was estimated from the dose, duration, and quality of vitamin D in supplements together with the 3-day average of dietary vitamin D at three time points over the pregnancy. Controlling for diet quality and total energy, maternal age, ethnicity, smoking, BMI, and gestational age, mothers with <5 μg/day intake bore infants whose birthweight was 60 g lower, on average, than for progeny of mothers with higher consumption ($p = 0.027$) (22) (Table 1).

In addition, four birth cohort studies examined the relationship between dietary vitamin D during pregnancy and childhood asthma or wheeze among progeny. In one study, data from food-frequency questionnaires collected during the eighth gestational month were used to evaluate maternal dietary and supplementary vitamin D intake (23). They also analyzed parent-report for childhood diagnosis of asthma, occurrences of wheezing, and medication treatment for asthma during the year prior to the child's fifth birthday. After controlling for maternal age, smoking, and diet, investigators showed that progeny of mothers with high vitamin D intake during pregnancy showed lower risk for asthma when compared to mothers with low intake ($OR = 0.76$, $p < 0.05$) (23) (Table 2).

Similarly, other data showed that the risk for wheezing during childhood is inversely related to dietary vitamin D during pregnancy (24-26). For example, one prospective cohort study gathered food-frequency questionnaire data at two time points over 40 weeks gestation for 1,194 women (24). Parent-report for frequency and duration of childhood wheezing was evaluated annually until the child's third birthday; children showing two or more episodes were classified as recurrent wheezers. After controlling for age and smoking during pregnancy, and parental history of asthma, they found that children of mothers with the highest quartile of vitamin D consumption were 2.6 times less likely than children of lowest-quartile mothers to show recurrent wheezing ($p < 0.001$) (24). Further, a test for trend indicates that there is an inverse dose-response relationship between vitamin D consumption during pregnancy and childhood recurrent wheezing ($p = 0.001$) (24) (Table 2).

A similar association was found among 1,212 women using prenatal services at a maternity hospital in Scotland (25). Maternal dietary vitamin D data were gathered using food-frequency questionnaires during the eighth month of pregnancy, and childhood wheezing data were gathered with questionnaires given at the child's second and fifth birthdays. After controlling for a number of covariates such as age and smoking during pregnancy, and parent-report for vitamin D intake in progeny at 5 years, they found that risk for wheeze decreased significantly as maternal dietary vitamin D increased. For example, mothers with the highest dietary vitamin D intake were 0.33 times as likely to have children with persistent wheeze (p = 0.01) (25) (Table 2).

Another birth cohort study in Japan found the same results for infants of 763 participants from the Osaka Maternal and Child Health Study (26). Maternal dietary vitamin D intake was measured using a diet history questionnaire, and parent-report of wheezing symptoms was obtained when the infant was 2-9 months old, and again at 16-24 months old. Maternal vitamin D intake was divided at the 25th percentile and after controlling for age, smoking during pregnancy, and smoking exposure, they found that children of mothers with dietary vitamin D intake above 4.309 µg/day were 0.64 (95% CI 0.43, 0.97) times as likely to be at risk for wheeze (26) (Table 2).

DISCUSSION

It appears that adequate or higher consumption of vitamin D during pregnancy may promote healthier birthweight overall. For example, cross-sectional and longitudinal data suggest 1.3-2% fold increase in infant birthweight among mothers with higher or adequate consumption, defined as meeting the *Recommended Daily Allowances* (RDA) of vitamin D. Sabour et al. reported that adequate consumption of calcium and vitamin D lowered the incidence of LBW (20); however, the size of the effect of consumption of vitamin D on the incidence of LBW is unclear since the authors did not report such data. Nevertheless, Watson and McDonald reported increased birthweight with maternal consumption of vitamin D (21). Similarly, Scholl and Chen found a linear trend between maternal dietary vitamin D and infant birthweight (22). Thus, maternal consumption of vitamin D can show positive health benefits for infant birthweight.

Nonetheless, these analyses may be limited as cross-sectional studies cannot determine causation. Thus both longitudinal cohort studies or randomized controlled trials may strengthen the understanding of the relationship between dietary vitamin D and birthweight outcomes. Second, some data suggest the effects of these nutrients on infant health may be short lived. Specifically, an association between vitamin D consumption and birthweight was measured at four months but unsustained after seven months of observation (21). In addition, the studies analyzed self-report data where serum analyses would be a better measure of vitamin D intake. Further, in processing dietary data using the USDA data base, which is limited to 600 foods, overestimation of consumption of vitamin D may have occurred (22). Last, findings from these observational studies largely pertain to low-income women who may have a myriad of exposures beyond dietary and supplemental vitamin D, making it difficult to easily generalize these findings to all pregnant women.

Current studies further suggest that higher vitamin D intake during pregnancy can lower the incidence of asthma and asthma-related symptoms in progeny. Erkkola et al. shows that maternal dietary vitamin D can lead to a 37% decrease in the prevalence of asthma in children at 5 years of age (23). Further, Devereux et al., Camargo et al. and Miyake et al. found that high maternal vitamin D intake is associated with a decreased prevalence of wheeze, a primary symptom of asthma, in children at 5 years, 3 years, and 16-24 months, respectively (22-24). Thus, these studies suggest that risk for asthma and asthma-related symptoms may increase with low levels of dietary vitamin D during gestation (23-26).

However, three of four studies report significant loss-to-follow-up, ranging from 22-34.9%, that may bias reported findings (23, 25, 26). Moreover, in two of these studies, there were significant differences among those lost to follow-up and those who completed the study (23, 25). Baseline data suggest that women who had lower intakes of vitamin D at the initial assessment, smoked, had a lower socioeconomic status, and lived a less healthy lifestyle were also less likely to complete the study, possibly introducing bias into the findings (23, 25). Another limitation of the studies is the inability to generalize the results to the public. The Camargo et al. and Miyake et al. studies experienced an overrepresentation of white mothers of high socioeconomic status and of mothers with high educational levels, respectively (24, 26). This combined with the potential for response bias, weakens the argument for maternal vitamin D's protective effect for childhood asthma.

Last, wheeze in early childhood may not be a good predictor of asthma (24-26). Some studies show that many children who have wheezing symptoms in the first few years of life do not have an increased risk of developing asthma later in life (27, 28). However, other studies show early childhood wheezing increases risk for developing chronic asthma (29, 30). Thus, data cannot conclusively support whether wheeze is an appropriate proxy indicator for child-onset asthma and findings must be interpreted with caution.

Conclusion

LBW continues to be a problem of concern as disorders related to LBW and preterm birth are the leading causes of infant mortality (31). Further, asthma is the number one cause of disability in children and can significantly limit a child's growth and development (17, 32, 33). From a review of studies, vitamin D supplementation in mothers increases birthweight, thereby suggesting a reduction of the incidence of LBW. Dietary vitamin D during pregnancy has also been linked to a decreased prevalence of childhood asthma and asthma-related symptoms. However, as randomized controlled trials offer the strongest evidence, it is recommended that such intervention studies be conducted to further determine the effect of dietary vitamin D during pregnancy on birthweight and asthma in progeny.

Table 1: Maternal dietary vitamin D and low birthweight

Study	Study Design	N	Target Population	Assessment Methods	Vit D Levels (Dietary)	Outcome Measures	Quantitative results (including statistical test results)
Sabour et al. (2006)	Cross-sectional study	449	Pregnant pregnant women and their newborns; Tehran, Iran; low SES; mean age: 25.87 (±5.1)	Food-frequency questionnaire; newborn measurements	Mean ± SD = 2.26 ±1.87 μg per day	Infant birthweight	Maternal and infant characteristics Maternal Prevalence (%) Adequate vit D [2]: 26.7 Calcium vit D supplements[3]: 33.8 Infant LBW [3] (overall): 5.2 LBW low Ca & vit D mothers> high intake mothers[4]: (statistics not provided) Apgar[5, 6]: 8.77 vs 8.61 [1]years; [2]Adequate=5 μg/day; [3]<2500 g; [4]p=0.007; [5]p=0.04; [6]Adjusted for maternal age, BMI, and energy and protein intake
Scholl & Chen (2009)	Cohort study	2,251	Pregnant women and their newborns; Camden, New Jersey; low SES; African American 37.4%, Hispanic 47.1%, Caucasian 14.8%; mean age: 22.01 (±0.11) y	24-hour recall interviews at baseline and weeks at 20 and 28 of gestation; infant medical records	Mean ± SE = 10.31 ± 0.089 μg per day	Infant birthweight	Maternal characteristics Mean infant birthweight by level of dietary vit D intake Maternal vit D [1] — Mean infant birthweight (SE) [2 3 4] <7.13 — 3163 (21) 7.13-9.20 — 3187 (20) 9.20-11.00 — 3193 (19) 11.00-13.38 — 3207 (19) >13.38 — 3228 (23)[5] [1]μg/day; [2] g; [3]Adjusted; [4] p for trend = 0.043; [5]2% higher than the <7.13 Controlling for energy intake, calcium, folate, iron, zinc, protein, age, parity, BMI, ethnicity, and gestational duration, mothers with vit D levels below RDA had infant birthweights 60 g lower on average than progeny of mothers with levels above RDA
Watson & McDonald (2010)	Cohort study	504	Pregnant women and their newborns; rural New	24-hour recall interview and 3-day food record at 4th and 7th months	Mean = 2.1 μg per day	Infant birthweight	Mean infant birthweight by maternal ethnicity Maternal ethnicity — n = — Mean infant birthweight (SD) [1 2] All — 439 — 3551 (544) European — 329 — 3551 (532)

			Zealand; stratified by race and ethnicity group;	of gestation; infant medical records			Maori 80 3467 (581) Pacific 30 3780 (528) [1] g, [2] p for trend = 0.026 - Controlling for gestational age, infant gender, maternal vit D intake at 4 months is associated with an increase in infant birthweight by 71 g, p = 0.015

Table 2: Maternal dietary vitamin D and asthma in progeny

Study	Study Design	N	Target Population	Assessment Methods	Vitamin D Levels (Dietary)	Outcomes measures	Quantitative results (including statistical test results)
Camargo et al. (2007)	Cohort study	1194	Pregnant women & their progeny; recruited from 8 obstetric offices in eastern MA in northeast US	Interviews & food frequency questionnaires at initial clinic visit, at 26-28 wks gestation, w/in 3 days of delivery, at 6 mo post-delivery, and annually thereafter; infant medical records	Mean = 548 ± 167 IU/d Mean intake from food = 225 IU Mean intake from suppl = 339 IU	Recurrent wheeze, defined as 2 or more wheezing attacks in the first 3 years of life	Maternal dietary vitamin D and OR for recurrent wheeze Quartiles of maternal dietary vitamin D: 1 / 2 / 3 / 4 Median (IU): 356 / 513 / 603 / 724 Recurrent wheeze, unadjusted[1]: 1 / 0.55 / 0.55 / 0.39 Recurrent wheeze, model 1[2]: 1 / 0.49 / 0.56 / 0.41 Recurrent wheeze, model 2[3]: 1 / 0.47 / 0.54 / 0.38 [1]p < 0.001; [2]p = 0.001, adjusted for age, smoking, BMI, breastfeeding duration, number of children <12 y, parental history of asthma, & birthweight; [3]p < 0.001, additionally adjusted for maternal diet
Devereux et al. (2007)	Cohort study	1212	Pregnant women & their progeny; Aberdeen Maternity Hospital, Scotland; purposeful sampling to include subjects with	Interviews, food frequency questionnaires at 32 wks gestation; asthma questionnaires at child's second & fifth birthday	Median energy-adjusted intake = 128 IU/d (n = 1751 mothers at baseline)	Wheeze, defined if parent reported child had wheezing in the previous year	Maternal dietary vitamin D and OR[*] for wheezing symptoms Quintiles of maternal dietary vitamin D: 1 / 2 / 3 / 4 / 5 Median (IU/d): 77 / 104 / 128 / 157 / 275 Ever wheeze[1]: 1 / 0.86 / 0.70 / 0.57 / 0.48 Wheeze in previous year[2]: 1 / 1.27 / 0.95 / 0.70 / 0.35

			non-western diets and demographics				Persistent wheeze[3] 1 1.10 0.63 0.43 0.33 *Adjusted for age, smoking, diet, education, social class, breastfeeding, and infant sex, birthweight, use of antibiotics, & vitamin D intake at 5 yrs p-values for trend across the quintiles: [1]p = 0.01; [2]p = 0.009; [3]p = 0.01
Erkkola et al. (2009)	Cohort study	1669	Pregnant women and their progeny enrolled in an existing study: Type 1 Diabetes Prediction & Prevention (DIPP) Study in Finland	Food frequency questionnaires immediately after delivery; asthma questionnaires at child's fifth birthday	Mean = 6.5 ± 3.8 μg/d	Asthma, defined if diagnosed by physician, had wheezing symptoms in previous year, or had used asthma medication in previous year	Maternal dietary vitamin D and HR for persistent asthma Vitamin D intake — Hazard ratio Energy-adjusted — 0.82* Energy-, maternal intake of vitamin C-, vitamin E-, selenium-, and zinc-adjusted — 0.76* *p < 0.05
Miyake et al. (2010)	cohort study	763	Japanese pregnant women & their children at 16-24 mos old; Recruited from municipalities of Osaka Prefecture, Japan; part of the Osaka Maternal and Child Health Study (OMCHS)	Diet history questionnaires at baseline; self-administered questionnaires when infant was 2-9 months old and 16-24 months old	Mean energy-adjusted intake = 6.2 ± 3.7 μg/d	Wheeze, defined if mother reported child had wheezing or whistling in chest in previous 12 months	Maternal dietary vitamin D and OR for wheeze Vitamin D — Odds ratio** < 4.309 μg/day* — reference value ≥ 4.309 μg/day — 0.64[1] *Maternal vitamin D intake was divided at 25th percentile (4.309 μg/day); **adjusted for age, smoking, diet, smoking exposure [1]95% CI 0.43-0.97

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