

Advances in the Study of the Association Between Vitamin D Intake During Pregnancy and the Risk of Autism Spectrum Disorders in the Fetus

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Abstract:

In recent years, studies on the association between vitamin D intake during pregnancy and the risk of autism spectrum disorder (ASD) in fetuses have attracted much attention. Vitamin D, a fat-soluble vitamin, not only plays a key role in calcium and phosphorus metabolism, but also affects neurodevelopment. Studies have shown that vitamin D insufficiency during pregnancy may lead to abnormal fetal brain development, thereby increasing the risk of ASD. This hypothesis is supported by several epidemiologic studies and animal experiments showing a significant association between vitamin D levels during pregnancy and fetal ASD risk. Nevertheless, the current study has some limitations, such as insufficient sample size, diversity in study design, and the influence of potential confounders. Therefore, more large-scale, prospective studies are needed in the future. This article reviews the effects of vitamin D intake during pregnancy on fetal ASD risk with the aim of increasing pregnant women's awareness of vitamin D supplementation during pregnancy.

Keywords:

Autism Spectrum Disorders, Pregnancy, Vitamin D, Vitamin D Deficiency

1. Introduction

1.1. Functional mechanisms of vitamin D

Vitamin D is a fat-soluble vitamin that is synthesized by the skin in response to ultraviolet radiation, and is also consumed through diet and supplements [1]. Its active form in the body is 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃), and its main functions include the regulation of calcium and phosphorus metabolism, the regulation of immune function, and the regulation of cell proliferation and differentiation [2]. The regulation of calcium and phosphorus metabolism is one of the most well known functions of vitamin D. It has been shown that vitamin D has the ability to regulate calcium and phosphorus metabolism in the intestine. By promoting intestinal

absorption of calcium and phosphorus, vitamin D plays a key role in maintaining blood calcium and phosphorus levels and promoting bone health [3]. Vitamin D also maintains calcium homeostasis in the body by working in concert with parathyroid hormone to regulate calcium release from the bones and calcium reabsorption by the kidneys [4]. In terms of immune function, vitamin D demonstrates a wide range of effects. It has been found that 1,25(OH)₂D₃ regulates a variety of functions of the innate and adaptive immune system. For example, vitamin D inhibits Th1 cell-mediated autoimmune responses while promoting the immune function of Th2 cells, thereby playing a protective role in a variety of autoimmune diseases [5]. The role of vitamin D in cell proliferation and differentiation is also of interest. 1,25(OH)₂D₃ not only regulates osteoblast formation and differentiation, but also plays a role in a variety of non-skeletal tissues. Studies have shown that vitamin D is potentially valuable in cancer prevention by regulating cell cycle and apoptosis [6]. In conclusion, the multiple functions of vitamin D in the human body make it a hot research topic.

1.2. Pathophysiologic Basis of Autism Spectrum Disorders

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder that usually presents in early childhood and is characterized by difficulties in social interaction, communication disorders and repetitive behaviors and interests [7]. Basic pathophysiological research suggests that the development of ASD may be related to a variety of genetic factors, neurodevelopmental abnormalities, immune system dysregulation, and environmental factors [8].

First, genetic factors play an important role in the development of ASD [9]. Numerous studies have shown a high degree of genetic heterogeneity in ASD, with siblings of children with ASD having a significantly higher risk of developing the disease than the general population, suggesting a clear genetic predisposition [10]. In addition, Genomic association studies (GWAS) have identified several genetic variants associated with ASD [11,12]. Mutations in genes such as SHANK3, NRXN1 and CHD8 are strongly associated with the development of ASD [13]. These genes are involved in key neurobiological processes such as synapse formation, neurotransmission and cytoskeletal organization.

Secondly, neurodevelopmental abnormalities are also an important pathophysiologic basis of ASD. Functional magnetic resonance imaging (fMRI) studies have shown abnormal connectivity between different regions of the brain in people with ASD, especially in brain regions related to social cognition [14]. The number of neurons and synaptic density may be abnormal in people with ASD, which may affect the normal functioning of the neural network [15].

Dysregulation of the immune system has also received extensive attention in the study of the pathophysiology of ASD. Patients with ASD have abnormal immune markers such as cytokines and autoantibodies in their blood and cerebrospinal fluid [16]. These abnormalities may reflect abnormal activation of the immune system or an autoimmune response. In addition, animal model studies have supported the role of the immune system in the development of ASD [17].

Environmental factors should not be ignored as well. Exposure to environmental toxins, drug use, and poor diet during pregnancy may increase the risk of ASD in the fetus [18]. In recent years, nutritional factors, particularly vitamin D deficiency, have been suggested to be possibly associated with the development of ASD, which is the factor that is the focus of this paper exploring progress Mothers with low vitamin D

levels during pregnancy have a significantly increased risk of ASD in their children . This may be due to the important role of vitamin D in neurodevelopment and the immune system [19].

In summary, the pathophysiologic basis of ASD is a complex, multifactorial process. Genetic factors, neurodevelopmental abnormalities, immune system dysregulation, and environmental factors work together, and future studies need to further reveal the mechanisms of interaction between these factors in order to better understand the etiology of ASD and provide new ideas for prevention and treatment.

2. Current Status of Domestic and International Literature

2.1. Studies on vitamin D intake and health during pregnancy

The role of vitamin D in health during pregnancy has become a hot topic of research in recent years. Many studies have examined the effects of vitamin D intake during pregnancy on maternal and fetal health. For example, vitamin D deficiency is significantly associated with the development of complications such as gestational hypertension, gestational diabetes, and preeclampsia in pregnant women [20]. And vitamin D not only affects the health of pregnant women, but also has a significant impact on fetal neurodevelopment, with studies suggesting that insufficient levels of vitamin D during pregnancy may be associated with the development of fetal neural tube malformations and other neurodevelopmental disorders [21]. A review analyzed several randomized controlled trials on vitamin D supplementation during pregnancy and found that appropriate vitamin D supplementation reduces the risk of complications in pregnant women and contributes to normal fetal development. Studies have emphasized the importance of vitamin D supplementation during pregnancy, especially in areas at high risk of vitamin D deficiency [22]. However, specific quantification of vitamin D intake and health benefits varies across studies. Meta-analyses of several studies have pointed out that factors such as the dose and frequency of vitamin D supplementation and the baseline vitamin D level of the pregnant woman can influence the heterogeneity of the findings. Nonetheless, most studies agree that appropriate intake of vitamin D has a positive effect on health during pregnancy [23]. In clinical practice, monitoring and supplementation of vitamin D levels has been incorporated into the standard process of health management during pregnancy [24].

In summary, a large number of studies have shown that vitamin D intake has an important impact on health during pregnancy, and that appropriate vitamin D supplementation can help reduce the risk of maternal complications and promote normal fetal development. However, the specific intake and supplementation should be adjusted on an individual basis.

2.2. Foreign studies on the association between vitamin D and autism

In recent years, a large number of foreign studies have revealed the important role of vitamin D in neurodevelopment and explored the relationship between its intake and the incidence of autism.

Cannell is the first to suggest that vitamin D deficiency may be an important risk factor for autism [25]. Their study, by analyzing various types of epidemiological data, found that the prevalence of autism in children was significantly increased in areas with vitamin D deficiency. The study triggered extensive academic attention and in-

depth research on this hypothesis. Related studies found that vitamin D has an important protective role in neurodevelopment. By analyzing the prevalence of autism and vitamin D levels in several countries, they found that the prevalence of autism is relatively higher in countries with lower vitamin D levels. In addition, they noted that vitamin D can reduce the risk of autism by modulating the immune system and reducing neuroinflammation [26]. This is further supported by another large cohort study conducted by Vinkhuyzen et al [27]. This study used data from the Danish National Birth Cohort and analyzed the relationship between vitamin D levels and autism risk in over 85,000 children. The results showed that children born to mothers with lower vitamin D levels during pregnancy had a significantly increased risk of autism. The study not only provides strong epidemiologic evidence, but also suggests the importance of vitamin D supplementation [28]. In addition, consistent with other studies, Kočovská and colleagues and Wang and colleagues [29,30] showed that reduced vitamin D levels during pregnancy and reduced solar UVB exposure may increase the risk of ASD. Meanwhile, Chen and colleagues [31] showed that maternal serum 25(OH)D levels were significantly lower in the autism group than in the neurotypical group, with 55.9% and 29.4% vitamin D deficiency, respectively. Lower maternal serum 25(OH)D levels early in pregnancy were associated with a significantly increased risk of autism in the offspring ($p < 0.001$). Fernell and colleagues [32] analyzed 25(OH)D in 58 pairs of Swedish-born siblings, where one child had ASD and the other did not. The children with ASD had significantly lower vitamin D levels than their siblings. This result reaffirms that vitamin D deficiency may be an important risk factor for autism.

Although the studies mentioned above provide a great deal of evidence supporting the association between vitamin D and autism, there is some controversy. A population-based study suggests that vitamin D deficiency in mothers may increase the risk of autism spectrum disorder (ASD), but direct evidence is lacking [33]. Overall, foreign studies generally support an association between vitamin D and autism, but the specific mechanisms and influencing factors need to be further explored.

2.3. Domestic explorations of the relationship between vitamin D and autism during pregnancy

There has also been a gradual increase in domestic research on the relationship between vitamin D intake during pregnancy and the risk of autism spectrum disorder (ASD) in the fetus, focusing on both survey and intervention studies. The following is a specific analysis of relevant domestic studies.

First of all, In a regional study in Shaanxi Province, a total of more than 300 children with autism and more than 300 children in general were surveyed, and blood was collected at different times to test the vitamin D levels in the children's blood. It was found that the percentage of insufficient and deficient vitamin D in autistic children was 34.5%, while the percentage of children in general was 21.8%. Both present a conclusion that the percentage of autistic children with vitamin D deficiency or insufficiency is higher than that of children in general [34].

Second, a meta-analysis of interventional studies, mainly a randomized controlled trial (RCT) [35], was conducted to examine whether vitamin D supplementation improves core symptoms and comorbid conditions in children with ASD. The results showed that vitamin D supplementation appeared to improve stereotypic behavior but

not other core symptoms and comorbidities, and that further randomized controlled trials with large sample sizes and individualized dosages are needed.

In addition, a domestic study further explored about the prevalence and risk factors of vitamin D deficiency in pregnant women in China, indicating that living in areas with low ambient outdoor UV levels increases the risk of vitamin D deficiency in women in late pregnancy, young pregnant women, and Hui women, and therefore, vitamin D supplementation and reasonable sunlight exposure should be encouraged, especially in the winter [36]. This study suggests that vitamin D deficiency monitoring and intervention should be strengthened for high-risk areas and populations.

Taken together, domestic studies on the relationship between vitamin D intake during pregnancy and fetal ASD risk have made some progress but still have some limitations. For example, the sample size is relatively small, the diversity of study designs is insufficient, and there is a lack of long-term follow-up data. Therefore, more large-scale, high-quality studies are needed in the future to validate these preliminary findings and to further clarify the mechanism of vitamin D's role in preventing ASD.

2.4. Impact of different regional and racial differences on the results of the study

It is critical to examine the impact of geographic and ethnic differences on the relationship between vitamin D intake and fetal autism spectrum disorder (ASD) risk. Multiple studies have shown that geographic location and ethnic background may significantly affect vitamin D levels, thereby creating discrepancies in findings on vitamin D intake during pregnancy and fetal ASD risk.

In North America, researchers have found that higher latitudes and fewer hours of sunshine may lead to more severe problems with vitamin D deficiency [37]. Shorter winter sunshine hours in North America lead to reduced vitamin D synthesis in pregnant women, which may contribute to the higher incidence of ASD in North America [38]. In Europe, findings show that there are also significant geographic differences in the association between vitamin D levels and ASD risk. Vitamin D deficiency is particularly problematic in the Nordic countries due to their high latitude and lack of solar radiation [39], which may increase the risk of ASD there. However, southern European countries such as Italy and Spain have relatively high levels of vitamin D in pregnant women due to abundant sunlight [40].

Racial differences also had a significant impact on the results of the study. Studies have found that dark-skinned people have a lower ability to synthesize vitamin D. This is due to melanin's ability to block ultraviolet light and reduce vitamin D production. Pregnant women of African descent have significantly lower levels of vitamin D than white pregnant women, which may contribute to the higher risk of ASD in children of African descent. In addition, pregnant women of Asian descent also have generally lower levels of vitamin D than white pregnant women, which is associated with a higher incidence of ASD in children of Asian descent [41].

In summary, different regional and racial differences have a significant impact on the results of the study of vitamin D intake and fetal ASD risk. Geographic factors such as sunlight hours and dietary habits, as well as racial factors such as skin pigmentation, can affect vitamin D levels in pregnant women and thus have an impact on the risk of ASD. Therefore, these differences need to be fully considered when

conducting relevant studies in order to draw more accurate and comprehensive conclusions.

3. Conclusions

3.1. Consensus and Controversy on Vitamin D Intake and Fetal Autism Risk

In this paper, a review and analysis of the relevant literature revealed a correlation between vitamin D intake in pregnant women and the risk of developing autism. Some studies clearly indicate that vitamin D supplementation during pregnancy plays a role in regulating the development and function of the nervous system, and studies conducted in vitro and in experimental animals suggest that vitamin D deficiency may be associated with the structural and functional abnormalities of the nervous system observed in patients with autism spectrum disorders [42,43]. However, there are also studies that question this conclusion. Although there is an association between low vitamin D levels during pregnancy and some neurodevelopmental abnormalities, there is no significant increase in autism risk. The study tested serum 25(OH) D in blood samples from 50 children diagnosed with ASD and 50 seemingly healthy children in the age group of 3 to 10 years. The results showed that vitamin D deficiency was prevalent in children with ASD and apparently healthy controls, with mean serum vitamin D being lower in children with ASD than in healthy controls, but the difference was not statistically significant [44]. Furthermore, at the mechanistic level, vitamin D acts as a steroid hormone that affects neuronal development and function through its receptors in the brain. Researchers generally agree with this mechanism, but the specific pathways of action and the degree of influence are still being explored [45]. Taken together, the correlation between vitamin D intake and autism in pregnant women still requires further research and study. For example, limitations such as insufficient sample size, poor study design, and inconsistent data collection methods have led to heterogeneity of findings and increased controversy between different studies' conclusions. In the future, more large-scale, multicenter prospective studies are needed to validate the existing findings and explore the specific pathways of vitamin D's role in fetal neurodevelopment.

3.2. Limitations of existing research and future research directions

There are several limitations in the existing research on vitamin D intake during pregnancy and fetal risk of autism spectrum disorder (ASD). First, there are significant differences in study design. Most studies used cross-sectional designs or case-control studies, and these designs make it difficult to clarify causality. Second, there was inconsistency in the methods and time points used to measure vitamin D levels. There were differences in the methods of measuring vitamin D levels used by different studies, with some studies relying on serum 25(OH)D concentrations, while others used dietary intake for estimation. In addition, the measurement of vitamin D levels at different time points in pregnancy also affects the comparison and synthesis of results. Changes in vitamin D levels during early, mid, and late pregnancy may have different effects on fetal development, and most studies failed to systematically cover the entire pregnancy. Differences in demographic characteristics and genetic background are also an important limiting factor. There are significant differences in vitamin D metabolism, dietary habits, and sunlight exposure among populations from different regions and ethnicities, and these factors may contribute to the heterogeneity of study results.

Future research needs to conduct more large-scale, longitudinal studies with long follow-up to clarify the causal relationship between vitamin D intake during pregnancy and the risk of fetal ASD. Such studies should consider multiple measurements of vitamin D levels to accurately reflect nutritional status throughout pregnancy. Studies should standardize the methods and time points for measuring vitamin D levels and consider geographic and ethnic differences. The comparability and comprehensiveness of results from different studies can be improved by standardizing measurement criteria and methods. The synergistic effects of vitamin D with other nutrients such as omega-3 fatty acids and folic acid should be further explored to gain a comprehensive understanding of the effects of nutrition during pregnancy on fetal neurodevelopment. By overcoming the limitations of existing studies, future research is expected to provide a more reliable scientific basis for optimizing vitamin D intake during pregnancy, thus providing effective intervention strategies for preventing fetal ASD risk.

3.3. Strategic Recommendations and Prevention Guidance

It is recommended that the wide dissemination and in-depth popularization of pregnancy health care knowledge should be strengthened in order to raise pregnant women's awareness of the importance of nutrition during pregnancy and the degree of importance they attach to it. Specialized nutritional guidance during pregnancy, systematic pregnancy health education and comprehensive counselling services should be provided to enhance pregnant women's awareness and ability to take care of themselves, which is of significant positive significance to the prevention of autism and other related diseases.

Regulatory measures should be strengthened during pregnancy, especially with regard to vitamin D intake, to ensure that pregnant women have access to adequate vitamin D intake. Greater attention should also be paid to the management of children's health, which, through early detection and timely intervention, can help to reduce the incidence of autism and improve the quality of life of those affected.

To further explore in depth the potential association between vitamin D intake in pregnant women and the development of autism, more high-quality clinical studies as well as cross-sectional surveys are recommended. This will provide a solid basis for the development of more scientific and effective autism prevention strategies in the future, and contribute significantly to the continued development of public health.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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