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Research Article

RESEARCH PROGRESS OF NEONATAL VITAMIN D DEFICIENCY

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ABSTRACT

Vitamin D is an essential fat-soluble vitamin in human body, it plays vital role in maintaining human health and normal cell growth and development, and affects the functions of many systems in human body. Vitamin D deficiency is very common in pregnant women and neonates, and is associated with common diseases such as neonatal hypocalcemia, neonatal respiratory distress syndrome, bronchopulmonary dysplasia, neonatal necrotizing enterocolitis and neonatal septicemia. At present, vitamin D deficiency is a global health problem. This article reviews the status of vitamin D deficiency in neonates and the research progress of the relationship between vitamin D deficiency and common diseases in neonates.

Key words: newborn, vitamin D, deficiency, neonatal diseases

INTRODUCTION

Vitamin D is a group of biologically active fat-soluble vitamins that can be synthesized endogenous, including vitamin D2 and vitamin D3. Vitamin D plays an important role in regulating the metabolism of calcium (Ca) -phosphorus (P) in human body. Vitamin D deficiency can cause rickets in children and osteomalacia in adults[1]. In addition, there is evidence that it is involved in the regulation of the immune system, lung development and differentiation of the nervous system[2]. Vitamin D deficiency is associated with a variety of diseases, and data show that low levels of 25-hydroxyvitamin D (25-OHD) are also associated with an increased risk of adverse pregnancy outcomes, such as pregnancy with diabetes, pre-eclampsia, perinatal infections, C-section, fetal growth restriction, etc.[3]. Low vitamin D level during pregnancy also has adverse effects on fetuses and neonates, including increased risk of premature delivery, low birth weight, low blood calcium and nervous system development lag, etc. Severe vitamin D deficiency may cause rickets, metabolic bone disease, cardiomyopathy and epilepsy in children[3]. It plays an important role in maintaining human health and normal cell growth and development[4]. Therefore, it is an important measure to improve the clinical outcomes of pregnant women and newborns to master the status quo of vitamin D levels of pregnant women and newborns in this region and take effective measures to prevent and treat vitamin D deficiency according to the situation.

Status of vitamin D deficiency:

Vitamin D deficiency is a recognized health problem worldwide, affecting approximately 1 billion people of all races and different ages worldwide. Asia, especially Middle East and Africa have been considered high-risk areas for deficiency, with particularly high prevalence observed in these continents[1, 5]. Several studies around the world have assessed the status of vitamin D in cord blood, have shown high rates of vitamin D deficiency in newborns, ranging from 28% in Poland over to 80% in Germany and Thailand[6]. It is reported the rate of vitamin D deficiency in preterm infants is 64% in the US, 83% in India and 63.7% in France[7]. A study conducted in Turkey have said more than half of it's population identified vitamin D deficiency, and more than half of the infants with intrauterine growth restriction lacked vitamin D[8]. Ataseven et al.[9] from the central Black Sea examined vitamin D in 152 preterm infants aged 29-35 weeks gestation, found 64% of them were severely vitamin D deficient. There have been several studies conducted on vitamin D level of pregnant women and newborns around the world. China is geographically large with vast diversity between north and south of China hence it lack of large sample and multi-center studies on the vitamin D level of pregnant women and newborns in China. Some studies are done of small-range and small-sample data surveys. An epidemiological survey of vitamin D levels in pregnant mothers and newborns was conducted in Beijing (N39° N), Mianyang (N30° N), Chengdu (N31° N), Lanzhou (N36° N), and Wuhan (N29° N) and showed the incidence of neonatal vitamin D deficiency varied with the location of samples[10]. Guan Lirong et al.[11]selected hospitalized neonates in Mianyang Central Hospital of Sichuan province as the research objects to analyze the basic vitamin D level of neonates in the inpatient wards and related influencing factors, and the results showed that nearly 96.6% of neonates were in low vitamin D level, which was much higher than that in North America and the Western Pacific region[12]. It can be seen that the rate of neonatal vitamin D deficiency is high and

common in China, but there are few studies on neonatal vitamin D level in related areas south of the Tropic of Cancer.

Factors associated with vitamin D deficiency:

There are three sources of neonatal vitamin D, namely, maternal placenta transport, skin synthesis with the help of sunlight, and intestinal absorption from food[13]. Due to the lack of outdoor activities, lack of adequate sunlight and single food source, the newborn receives less vitamin D through food, so the transport through maternal placenta becomes the main source of vitamin D for the newborn[8]. Multiple studies at home and abroad have shown that maternal and neonatal 25-OHD levels are highly correlated, and there is a strong relationship between maternal and fetal (umbilical cord blood) circulating 25OHD levels, so maternal vitamin D deficiency can largely cause neonatal vitamin D deficiency[14]. Domestic studies have found that the 25-OHD level of newborns is related to the birth season. The 25-OHD level of preterm infants and full-term infants born in summer and autumn are higher than that of those born in winter and spring, which may be related to the low vitamin D self-synthesis level of pregnant mothers due to the lack of adequate sunlight exposure in winter and spring[15]. McCarthy et al.[16] found that the vitamin D level of premature infants is highly correlated with gestational age, and the vitamin D level of newborns with a gestational age of less than 32 weeks is generally lower than that of newborns over 32 weeks of gestational age. However, there was no correlation between 25-OHD level of newborns in terms of birth weight, gender, single or twin, small gestational age, blood collection age, etc.

Relationship between vitamin D deficiency and neonatal related diseases:

Neonatal hypocalcemia:

Hypocalcemia is a very common disorder of electrolyte metabolism in the neonatal period. It has been reported that the prevalence of neonatal hypocalcemia is relatively high, and its incidence is correlated with gestational age of newborn, perinatal vitamin D level of pregnant mother and complications during pregnancy[17]. The main function of vitamin D is to regulate the balance of calcium and phosphorus metabolism in the body and increase the intestinal absorption of calcium, renal reabsorption of calcium and bone calcium released into the blood, so as to improve the level of blood calcium. Studies shows, neonates with low vitamin D levels are likely to develop hypocalcemia after birth. High level of vitamin D during pregnant mother, the levels of serum total calcium and calcium ion were higher than those of vitamin D deficient mothers[18]. Vitamin D deficiency and hypocalcemia are common in neonates. Several studies and scientific guidelines suggest, pregnant women should take regular vitamin D supplements during pregnancy and after birth to reduce the incidence of vitamin D deficiency and hypocalcemia in neonates. Studies suggest to have routinely check of vitamin D, serum calcium and ionized calcium especially for pregnant women, lactating women and newborns to detect and prevent vitamin D deficiency and hypocalcemia early[19].

Neonatal respiratory distress syndrome:

Neonatal respiratory distress syndrome (NRDS) is a common in newborn seen immediately after delivery. Although treatment methods such as prenatal corticosteroids, surfactants and advanced respiratory support for newborns have improved the outcome of NRDS. Despite of all it is still a major cause of premature morbidity and mortality[20]. The main cause of NRDS is the loss of alveolar surfactant. At present, many animal experiments have shown that vitamin D has a positive effect on the proliferation of alveolar type II epithelial cells (ATII) and fibroblasts, and the synthesis of surfactants. Marin et al. [20] believed that 1,25(OH)2D3 accelerated the decrease of glycogen content in ATII cells of fetal rat lungs and increased the synthesis and secretion of surfactant-related phospholipids. Zheng et al.[21] verified the role of vitamin D in stimulating epithelial cell injury repair and reducing primary ATII cell apoptosis in vitro experiments. In addition, vitamin D promoted primary ATII cell proliferation through P13K/AKT signaling pathway and activation of vitamin D receptor (VDR). Together, these results suggest the therapeutic potential of vitamin D for NRDS. The following clinical studies further verified the relationship between vitamin D and NRDS. Adham et al. [22] investigated the serum vitamin D level of 65 premature infants and found that the vitamin D level of the NRDS group was significantly lower than that of the control group. Further logistic regression analysis showed that low serum 25 (OH) D level was an independent risk factor for RDS. Chinese scholar Yu Yang's study also verified similar conclusion. The author retrospectively analyzed the clinical data of 60 children with NRDS and 60 healthy newborns, and found that low serum level of 1, 25-dihydroxyvitamin D3 in pregnant women is closely related to the occurrence of neonatal respiratory distress syndrome[23].

Bronchopulmonary dysplasia:

Bronchopulmonary dysplasia (BPD) is a chronic lung disease closely related to preterm birth, characterized by interrupted lung development in the preterm baby. At present, many animal experiments have confirmed the positive role of vitamin D in lung development, thus producing a protective effect on BPD. Chengbo Liu et al. [24] established a BPD rat model by intra-amniotic injection of lipopolysaccharide (LPS), and the experimental results showed that Vitamin D could effectively alleviate the simplification of alveolar structure in BPD rats and inhibit the expression of IFN-γ in lung tissues induced by lipopolysaccharide. In the study of LI YAO et al. [25], vitamin D can antagonize the activation of TLR4 induced by high oxygen, thus relieving inflammation and reducing cell apoptosis, thus protecting the alveolar structure. Many scholars have further verified the relationship between vitamin and BPD through clinical studies. In a prospective study of 132 premature infants ≤32 weeks reported by Turkish scholar Cetinkaya, the level of 25(OH)D in pregnant women and neonates in the BPD group was significantly lower than that in the non-BPD group[26]. Similarly, Chinese scholars[27] investigated the level of vitamin D in umbilical cord blood of 133 premature infants admitted to the Department of Neonatology of Shijiazhuang Fourth Hospital from May 2018 to April 2020, and found that compared with the non-BPD group, the level of vitamin D in grade I, II and III BPD patients gradually decreased. More importantly, levels of umbilical cord blood vitamin D were significantly lower in the grade II and III groups than in the non-BPD groups, and further survival analysis found that vitamin D less than 30 nmol/L was

a risk factor for comprehensive outcome or death from BPD. In general, low vitamin D levels in preterm infants may increase the incidence of BPD and be associated with the severity of BPD [28, 29].

Neonatal necrotizing enterocolitis (NEC):

Neonatal necrotizing enterocolitis is a serious gastrointestinal disease mainly occurring in premature infants. Although its pathogenesis is still unclear, some studies have reported that intestinal epithelial barrier dysfunction is an important link in the occurrence of NEC[30]. However, Du J et al. [31] conducted an animal experiment on the induction of trinitrophenylsulfuric acid in NEC. The author found that vitamin D regulates myosin light chain kinase (MLCK) to protect intestinal epithelial barrier function through VDR signaling pathway. It improves trinitrophenylsulfate induced colitis. Similarly, the animal experiment results of Shi Yongyan et al.[32] showed that vitamin D-treated NEC rats had significantly reduced intestinal cavity structure destruction, submucosal or muscular separation and other pathological manifestations, while immunofluorescence and western blot results showed that vitamin D treatment could increase the expression of closed protein. Therefore, the authors speculate that vitamin D may inhibit the development of NEC by up-regulating the expression of intestinal epithelial tight junction related proteins. The relationship between vitamin D and NEC has also been demonstrated in clinical trials. Yang L R et al.[33] investigated the serum 25-OHD levels of 429 premature infants and their mothers, and found that the serum 25-OHD levels of mothers and premature infants in the NEC group were significantly lower than those in the non-NEC group. Univariate Logistic regression analysis showed that the 25-OHD levels of mothers and premature infants were risk factors for the occurrence of NEC.

Neonatal sepsis:

Neonatal septicemia is one of the most common diseases in neonatal intensive care unit. Chiesa et al.[34] and Cetinkaya et al.[35] showed in their studies on the relationship between vitamin D and immune system that vitamin D is involved in human immune regulation, mainly through the binding of 1,25(OH)2 vitamin D with vitamin D receptor, thus playing an immune regulatory role. Vitamin D can increase the phagocytosis and motor functions of macrophages and neutrophils. It increases the ability of the body to phagocytosis bacteria, inhibit the over expression of inflammatory factors by monocytes and promote the balance of pro-inflammatory and anti-inflammatory cytokines Hence reducing inflammatory response[35]. Singh and Chaudhari[36] showed that vitamin D supplementation helped reduce sepsis scores and inflammatory cytokine levels in patients with early-onset sepsis who were given effective antibiotics. Agrawal et al.[37] found that among full-term newborns, vitamin D level in healthy newborns without sepsis was higher than that in children with sepsis, and the risk of sepsis in the vitamin D deficient group was higher than that in the newborn with normal vitamin D level. These studies have shown that vitamin D deficiency is closely associated with neonatal sepsis, and newborns with vitamin D deficiency are more likely to develop neonatal sepsis.

Prevention and treatment of neonatal vitamin D deficiency:

At present, there is no completely unified standard plan for vitamin D supplementation for pregnant women and newborns around the world, which may be related to the different rates and degrees of vitamin D

deficiency in different regions[38]. In response to concerns about widespread vitamin D deficiency in children, doctors recommend 400 international units of vitamin D daily[38]. In 2010, the European Association of Paediatric Gastroenterology, Hepatology and Nutrition recommended daily supplementation of vitamin D of 800-1000 IU for premature infants[39]. The 2016 Global Consensus on the Prevention and Management of Nutritional rickets recommended daily supplementation of vitamin D 200-400 IU with a maximum of 1000 IU/d[40]. In China, recommendations on prevention and Treatment of Vitamin D Deficiency and Vitamin D deficient rickets in 2015[41] proposed: High-risk infants, such as premature infants, low-birth-weight infants and twin fetuses should start vitamin D supplementation as soon as possible after birth with 800~1000 IU/ D, then change to 400~800 IU/ D after 3 months of continuous use, and infants should start vitamin D supplementation with 400-800U/ D as soon as possible after birth. However, early preterm infants (EPTIs) may be at risk of low vitamin D status due to the prevalence of vitamin D deficiency in pregnant women, lack of outdoor activities during childbirth, insufficient sunlight exposure, and inadequate dietary nutrition during hospitalization. More investigations and studies are needed to confirm whether the supplementation recommended by various guidelines can effectively improve neonatal vitamin D deficiency[42]. In recent years, due to the increasing living standards, gradually improve the maternal preventive care clinics, cognition of vitamin D for people gradually improve, vitamin D detection and the use of vitamin D supplements increased dramatically. At present vitamin D supplement is a debatable topic regarding the optimal dose[38]. Natarajan et al.[43] conducted a randomized controlled study on supplementation of different doses of vitamin D (400 and 800IU/ D) for preterm infants at gestational age of 28-34 weeks, and the results showed that even if preterm infants were given oral supplementation of vitamin D800IU/ D, their vitamin D level still did not reach the ideal standard at 40 weeks of corrected gestational age. Another study on oral supplementation of three different doses of vitamin D (400, 800 and 1 000 IU/ D) to premature infants and a domestic study on routine oral supplementation of vitamin D to premature infants of 900 IU/ D both showed that the vitamin D deficiency rate was still over 30% at the 28th day after birth[2]. The above studies indicate that the current vitamin D supplementation regimen cannot fully meet the vitamin D needs of all newborns, especially premature infants.

CONCLUSION

Vitamin D is closely related to human health, and vitamin D deficiency is prevalent in newborn population. Many studies have confirmed that vitamin D deficiency is related to common diseases of newborn, so it is particularly important to prevent and treat vitamin D deficiency. At present, there is no completely unified vitamin D supplement program at home and abroad, so it has great significance to actively explore the methods, timing and dosage of vitamin D supplement for neonates, especially those who are premature and suffering from post-natal diseases.According to some statistics, the deficiency of vitamin D in newborns and their mothers, especially premature infants, is a serious health care problem that needs to be standardized.

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