A Study on the Relationship of Vitamin A and E Levels in Umbilical Cord Blood with Respiratory Distress Syndrome in Preterm Infants (Postprint)

Authors: LIU Weina, GE Haiyan, MA Jing, CAO Qinying, BAI Xingyu, Shifang Cui, QIAO Yanxia, QIAO Yanxia

Date: 2023-10-09T00:00:00+00:00

Abstract

Background Respiratory distress syndrome (RDS) is a major cause of mortality in preterm infants, requiring continuous improvement in clinical prevention and treatment. However, the relationship between umbilical cord blood vitamin A and E levels and the development of RDS in preterm infants has been rarely reported. Objective To investigate the relationship between vitamin A and E levels in umbilical cord blood and RDS in preterm infants. Methods A total of 304 preterm infants admitted to the Fourth Hospital of Shijiazhuang from January 2021 to January 2022 were enrolled and divided into an RDS group (n=120) and a non-RDS group (n=184) based on the diagnosis of RDS. Clinical features potentially related to the occurrence of RDS in preterm infants were collected, and vitamin A and E levels in umbilical cord blood were measured. Multivariate logistic regression analysis was used to analyze the influencing factors of the occurrence and severity of RDS in preterm infants. Results The gestational age, birth weight, and vitamin A and E levels in umbilical cord blood of preterm infants in the RDS group were lower than those in the non-RDS group, while the proportions of one-minute Apgar score $\leq$ 7, five-minute Apgar score $\leq$ 7, and the incidence of vitamin A deficiency were higher in the RDS group than in the non-RDS group ($P<0.05$). In the RDS group, there were 86 cases of mild RDS and 34 cases of severe RDS; the vitamin A level in umbilical cord blood in severe RDS cases was significantly lower than in mild RDS cases, while the incidence of vitamin A deficiency was significantly higher than in mild RDS cases ($P<0.05$). Multivariate logistic regression analysis showed that vitamin A level in umbilical cord blood was an influencing factor for the occurrence of RDS in preterm infants [OR=2.208, 95%CI (1.156, 4.218), $P<0.05$], and vitamin A deficiency was an influencing factor for the occurrence of severe

RDS [OR=6.835, 95%CI (2.537, 18.416), P<0.05]. Conclusion Vitamin A and E levels in umbilical cord blood are relatively lower in preterm infants with RDS, and vitamin A level is an influencing factor for the occurrence and severity of RDS in preterm infants, suggesting that vitamin A supplementation should be administered during pregnancy to reduce the occurrence or severity of RDS in preterm infants.

Full Text

Preamble

A Study on the Relationship of Vitamin A and E Levels in Umbilical Cord Blood with Respiratory Distress Syndrome in Preterm Infants

LIU Weina[1], GE Haiyan[1], MA Jing[1], CAO Qinying[2], BAI Xingyu[1], CUI Shifang[1], QIAO Yanxia[1]*

[1]Department of Neonatology, the Fourth Hospital of Shijiazhuang, Shijiazhuang 050000, China
[2]Shijiazhuang People' s Hospital, Shijiazhuang 050000, China

*Corresponding author: QIAO Yanxia, Chief physician; E-mail: qyx19631961@126.com

Abstract

Background: Respiratory distress syndrome (RDS) is an important cause of death in preterm infants that requires continuous strengthening of clinical prevention and treatment, yet the relationship between umbilical cord blood vitamin A and E levels and the development of RDS in preterm infants has been rarely reported.

Objective: To investigate the relationship between vitamin A and E levels in umbilical cord blood and RDS in preterm infants.

Methods: A total of 304 preterm infants delivered at the Fourth Hospital of Shijiazhuang from January 2021 to January 2022 were selected and divided into an RDS group (n=120) and a non-RDS group (n=184) according to RDS incidence. Clinical features potentially related to RDS occurrence were collected, and vitamin A and E levels in umbilical cord blood were measured. Multivariate logistic regression analysis was used to analyze influencing factors for the occurrence and severity of RDS in preterm infants.

Results: Gestational age, birth weight, and umbilical cord blood levels of vitamins A and E in the RDS group were lower than those in the non-RDS group, while the proportions of infants with 1-minute Apgar score $ $7, 5-minute Apgar score $ $7, and the incidence of vitamin A deficiency were higher in the RDS group (P<0.05). Among the RDS group, there were 86 mild cases and 34 severe cases. The umbilical cord blood vitamin A level in severe RDS cases was significantly lower than in mild cases, while the incidence of vitamin A deficiency was significantly higher (P<0.05). Multivariate logistic regression

analysis showed that umbilical cord blood vitamin A level was an influencing factor for RDS occurrence in preterm infants [OR=2.208, 95%CI (1.156, 4.218), P<0.05], and vitamin A deficiency was an influencing factor for severe RDS occurrence [OR=6.835, 95%CI (2.537, 18.416), P<0.05].

Conclusion: Vitamin A and E levels in umbilical cord blood are relatively lower in preterm infants with RDS, and vitamin A level is an influencing factor for both the occurrence and severity of RDS in preterm infants, suggesting that vitamin A supplementation during pregnancy may reduce the incidence or severity of RDS in preterm infants.

Keywords: Respiratory distress syndrome, newborn; Infant, premature; Fetal blood; Vitamin A; Vitamin E; Risk factors

Introduction

Neonatal respiratory distress syndrome (RDS) is the main clinical manifestation of respiratory distress occurring shortly after birth, characterized by progressive respiratory distress followed by hypoxia and acidosis. RDS is most common in preterm infants and represents a major cause of serious neonatal complications such as bronchopulmonary dysplasia and death. Pulmonary surfactant (PS) deficiency is the primary cause of RDS. Since alveoli first appear in the fetus at 25 weeks of gestational age, lung development continues with increasing alveolar number until stabilization at 36 weeks, when type II epithelial cells in the alveoli begin to secrete PS. Consequently, the younger the gestational age, the higher the RDS incidence. One study showed that RDS incidence was 4.6% in neonates at 35 weeks of gestational age, decreasing to 1.6% at 36 weeks [1].

Vitamins A and E are fat-soluble essential vitamins. FERNANDES-SILVA et al. [2] demonstrated that retinoic acid, the main active form of vitamin A, plays an important regulatory role in lung development and alveolar formation, and vitamin A deficiency is associated with various lung diseases [3]. KOLLECK et al. [4] showed that vitamin E is involved in alveolar type II epithelium and is an indispensable component of PS synthesis, being secreted together with PS into the interalveolar space. Currently, clinical studies on the relationship between vitamins and neonatal RDS have mainly focused on serum vitamin A levels, which have not been fully clarified, while studies on vitamin E and neonatal RDS have been less frequently reported. Since neonatal RDS mostly occurs within 6 hours after birth, we chose to collect umbilical cord blood from preterm infants at birth to measure vitamin A and E levels, thereby avoiding the influence of postnatal diseases or clinical treatment. This study investigated the relationship between umbilical cord blood vitamin A and E levels and RDS in preterm infants to provide a reference for clinical prevention and treatment of RDS in this population.

1. Objects and Methods

1.1 Research Subjects

A total of 304 preterm infants born in the Fourth Hospital of Shijiazhuang from January 2021 to January 2022 were selected and divided into an RDS group (n=120) and a non-RDS group (n=184) according to RDS occurrence. Inclusion criteria: (1) gestational age <36 weeks; (2) cord blood collection from the fetal end completed immediately after umbilical cord clamping; (3) guardians of preterm infants were informed of the purpose of cord blood examination and provided signed informed consent; (4) prenatal examinations of the mothers revealed no congenital diseases such as complex congenital heart disease or chromosomal disorders. Exclusion criteria: (1) congenital diseases such as congenital diaphragmatic hernia or metabolic diseases discovered after birth; (2) pulmonary hemorrhage, pneumothorax, or diaphragmatic hernia appearing immediately after birth; (3) mothers suffering from chronic liver or kidney diseases. This study was approved by the Ethics Committee of the Fourth Hospital of Shijiazhuang City (approval number: 20230089).

1.2 Diagnostic and Grading Criteria for RDS in Preterm Infants

Diagnosis followed the criteria for neonatal RDS in *Practical Neonatology* (5th edition) [5]: (1) Clinical manifestations: progressive dyspnea and severe hypoxic respiratory failure appearing immediately after birth; (2) Chest X-ray findings: uniformly distributed lesions with decreased lung translucency in early stages showing a "ground-glass" appearance, and in severe cases, the entire lung field showing a "white lung" appearance with visible bronchial air trapping signs.

Grading criteria for RDS in preterm infants: Grade I—decreased lung translucency with fine granular reticular shadows in the lung field and clear cardiac silhouette; Grade II—further aggravation based on Grade I with obvious bronchial inflation extending to the middle lung fields; Grade III—continued aggravation based on Grade II with prominent bronchial inflation signs, poorly defined cardiac and diaphragmatic shadows, and "ground-glass" changes throughout the lung field; Grade IV—very severe lesions with obvious bronchiectasis signs and "white lung" appearance throughout the lung field but no thoracic or diaphragmatic lesions. In this study, RDS grades I-II were defined as mild cases, and grades III-IV as severe cases.

1.3 Treatment

All preterm infants received treatment within 12 hours after birth. The non-RDS group received nutritional support and symptomatic treatment, while the RDS group received respiratory support with appropriate ventilator modes based on respiratory conditions in addition to nutritional support and symptomatic treatment. For high-risk preterm infants who breathed spontaneously after birth but might develop RDS (e.g., <30 weeks gestational age not requiring intubation and mechanical ventilation), or those receiving oxygen via nasal cannula,

mask, or hood with inspired oxygen concentration (FiO_2) >0.3, arterial partial pressure of oxygen <50 mmHg (1 mmHg=0.133 kPa), or transcutaneous oxygen saturation ($TcSO_2$) <90%, continuous positive airway pressure was administered with positive end-expiratory pressure $ 6*cmH{2}O*(1*cmH{2}O = 0.098*kPa*), *oxygen flow rate of* 6–8*L/min*, *and FiO*_{2}$ adjusted according to $TcSO_2$. For preterm infants without spontaneous respiration after birth, non-invasive ventilator assistance was used when FiO_2>0.6, arterial partial pressure of oxygen <60 mmHg, or $TcSO_2$<85%, and arterial partial pressure of carbon dioxide >60 mmHg with persistent acidosis (pH<7.2). When acidosis (pH<7.2) was present, the ventilator was switched to invasive ventilation using synchronized intermittent mandatory ventilation mode with initial parameters: peak inspiratory pressure 20–25 cmH_2O, positive end-expiratory pressure 4–6 cmH_2O, respiratory rate 30–40 breaths/min, inspiratory time 0.3–0.4 s, and tidal volume 4–6 mL/kg. When $FiO_2$$ $0.3 under invasive or non-invasive ventilation, 40–100 mg/kg of bovine lung surfactant (manufacturer: China Resources Shuanghe Pharmaceutical Co., Ltd., batch no.: 2011994) was administered intratracheally as alternative treatment.

1.4 Observation Indexes

A designated researcher collected clinical characteristics potentially related to RDS occurrence, including maternal and infant conditions. Maternal conditions involved age, delivery mode, prenatal hormone application, premature rupture of membranes >18 hours, and incidence of gestational diabetes mellitus, gestational hypertension, and chorioamnionitis. Infant conditions involved gestational age, birth weight, sex, 1-minute Apgar score $ $7, 5-minute Apgar score $ $7 (according to diagnostic criteria for neonatal asphyxia [5-6], these are necessary conditions), umbilical cord blood vitamin A and E levels, and vitamin A and E deficiency status. Diagnostic criteria for vitamin A and E deficiency: Referring to WHO 2011 criteria and previous studies [7-8], cord blood vitamin A level <100.0 g/L was considered vitamin A deficiency, and <200.0 g/L was considered subclinical vitamin A deficiency.

1.5 Detection Method for Umbilical Cord Blood Vitamin A and E Levels

Three milliliters of umbilical cord blood was extracted from the fetal end after cord clamping, placed in test tubes without anticoagulant, stored at 0–4°C protected from light, and centrifuged for 15 minutes (radius: 10 cm) to isolate serum. After protein and impurity removal, active ingredients were extracted with n-hexane, resolubilized in methanol, and analyzed using Agilent UPLC1290 high-performance liquid chromatography to detect vitamin A and E levels and generate data curves. Error calibration was not allowed to exceed 15%, and final results were validated using the Westgard multi-rule quality control method.

1.6 Statistical Methods

Data were analyzed using Excel and SPSS 25.0 software. Normally distributed measurement data were expressed as ($\bar{x}\pm s$) and compared between groups using independent samples t-test. Non-normally distributed measurement data were expressed as M(P_{25}, P_{75}) and compared using Mann-Whitney U test. Count data were expressed as relative numbers and compared using ^{2} test or Fisher' s exact probability method. Multivariate logistic regression analysis was used to analyze factors affecting RDS occurrence and severity. $P<0.05$ was considered statistically significant.

2. Results

2.1 Comparison of Clinical Characteristics Between the Two Groups

Differences in maternal age, delivery mode, prenatal hormone use, premature rupture of membranes >18 hours, and incidence rates of gestational diabetes mellitus, gestational hypertension, and chorioamnionitis were not statistically significant ($P>0.05$), as shown in Table 1 .

In the RDS group, gestational age and birth weight were lower than in the non-RDS group, the proportions of infants with 1-minute Apgar score $ $7 and 5-minute Apgar score $ $7 were higher, and umbilical cord blood vitamin A and E levels were lower, with statistically significant differences ($P<0.05$). There was no statistically significant difference in infant gender between the two groups ($P>0.05$), as shown in Table 2 .

2.2 Comparison of Vitamin A and E Deficiencies Between the Two Groups

The incidence of vitamin A deficiency in the RDS group was 25.0% (30/120), higher than the 13.0% in the non-RDS group, with a statistically significant difference (^{2}=7.108, P=0.008). The incidence of subclinical vitamin A deficiency was 70.8% (85/120) in the RDS group and 69.6% (128/184) in the non-RDS group, with no statistically significant difference (^{2}=0.056, P=0.813). The incidence of vitamin E deficiency was 92.5% (111/120) in the RDS group and 91.3% (168/184) in the non-RDS group, with no statistically significant difference (^{2}=0.138, P=0.004).

2.3 Multivariate Logistic Regression Analysis of Factors Affecting RDS Development in Preterm Infants

Using RDS development as the dependent variable (assigned: yes=1, no=0) and observation indexes showing statistically significant differences in univariate analysis as independent variables [gestational age (assigned: measured value), birth weight (assigned: measured value), 1-minute Apgar score $ $7 (assigned: yes=1, no=0), 5-minute Apgar score $ $7 (assigned: yes=1, no=0), cord blood

vitamin A level (assigned: measured value), cord blood vitamin E level (assigned: measured value)], multivariate logistic regression analysis showed that gestational age, birth weight, and cord blood vitamin A level were influencing factors for RDS occurrence (P<0.05), as shown in Table 3 . After correcting for gestational age and birth weight, cord blood vitamin A level remained an influential factor [OR=2.208, 95%CI (1.156, 4.218), P<0.05].

2.4 Comparison of Cord Blood Vitamin A and E Levels and Deficiencies by RDS Severity

In the RDS group, 86 preterm infants had mild RDS and 34 had severe RDS. Cord blood vitamin A level in severe RDS cases was lower than in mild cases, and the incidence of vitamin A deficiency was higher, with statistically significant differences (P<0.05). There were no statistically significant differences in cord blood vitamin E level, subclinical vitamin A deficiency, or vitamin E deficiency between different RDS severity levels (P>0.05), as shown in Table 4 .

2.5 Multivariate Logistic Regression Analysis of Factors Influencing RDS Severity

Using infants without RDS as reference and mild RDS as the dependent variable (assigned: yes=1, no=0), with gestational age (assigned: measured value), birth weight (assigned: measured value), 1-minute Apgar score $ $7 (assigned: yes=1, no=0), 5-minute Apgar score $ $7 (assigned: yes=1, no=0), and vitamin A deficiency (assigned: yes=1, no=0) as independent variables, multivariate logistic regression analysis showed that gestational age was an influencing factor for mild RDS development (P<0.05), as shown in Table 5 .

Using infants without RDS as reference and severe RDS as the dependent variable (assigned: yes=1, no=0), with gestational age (assigned: measured value), birth weight (assigned: measured value), 1-minute Apgar score $ $7 (assigned: yes=1, no=0), 5-minute Apgar score $ $7 (assigned: yes=1, no=0), and vitamin A deficiency (assigned: yes=1, no=0) as independent variables, multivariate logistic regression analysis showed that birth weight and vitamin A deficiency were influencing factors for severe RDS development (P<0.05), as shown in Table 6 .

3. Discussion

Current clinical treatment for RDS in preterm infants is based on ventilatory support and PS replacement therapy; however, treatment of severe RDS is more difficult and expensive, with greater possibility of sequelae such as bronchopulmonary dysplasia. Since RDS is a main cause of death in preterm infants, understanding factors influencing RDS development and implementing targeted prevention are important to minimize RDS occurrence, especially severe RDS, improve clinical prognosis, and reduce morbidity and mortality.

Studies have shown that RDS occurrence in preterm infants is influenced by

many factors [9-11], among which low birth weight is a risk factor across different gestational ages [12]. This study found through multivariate logistic regression analysis that gestational age and birth weight were influencing factors for RDS occurrence, consistent with these findings.

In recent years, studies on vitamins A, D, and E in neonatal diseases have attracted much attention [13-15]. While vitamin D has been more extensively studied, fewer reports have examined the relationship between vitamins A and E and RDS in preterm infants. Vitamin A is a fat-soluble vitamin necessary for epithelial cell growth and development. Studies show that vitamin A deficiency is not only related to many diseases in preterm infants [16] but also plays important roles in various stages of lung development, such as regulating retinoic acid receptors in lung tissue and up-regulating SP-B gene expression to directly promote PS synthesis [17]. Animal experiments demonstrate that vitamin A can promote fetal lung maturation, with early gestational deficiency leading to poor fetal lung development and late gestation deficiency causing defective alveolar formation [18-19]. Meng Jun et al. [20] showed that serum vitamin A levels were significantly lower in the RDS group than in the non-RDS group, while Dai Yuqing et al. [21] found no statistically significant differences in serum vitamin A levels among preterm infants of different gestational ages and birth weights. Our results showed that the RDS group had lower gestational age and birth weight, higher proportions of infants with 1-minute and 5-minute Apgar scores $ $7, and lower umbilical cord blood vitamin A levels than the non-RDS group. Multivariate logistic regression analysis showed that gestational age, birth weight, and cord blood vitamin A level were influencing factors for RDS occurrence.

Recent studies on vitamin A and neonatal RDS have increased. ELFARARGY et al. [22] showed that serum vitamin A levels in infants with RDS grades III-IV were significantly lower than in non-RDS newborns. JIANG Xue [23] found that serum vitamin A levels in RDS infants at 34–36 weeks gestational age were lower than in non-RDS preterm infants, but did not correlate with RDS severity. Other studies showed no correlation between serum vitamin A levels and neonatal RDS [24-25]. Therefore, we measured vitamin A and E levels in umbilical cord blood at birth and found that cord blood vitamin A levels in severe RDS cases were lower than in mild cases, with higher vitamin A deficiency incidence. Further multivariate logistic regression analysis revealed that vitamin A deficiency was not an influencing factor for mild RDS but was a factor for severe RDS, suggesting that vitamin A deficiency has greater influence on severe RDS development.

Vitamin E, also known as tocopherol, has been studied primarily as α-tocopherol and γ-tocopherol. Animal experiments showed that maternal supplementation with α- and γ-tocopherols accelerated lung growth and improved pulmonary dysplasia and vascular remodeling in rat fetuses, suggesting vitamin E plays an important role in lung development [26]. A randomized controlled trial by RUMBOLD et al. [27] including 1,877 women showed that neonatal RDS inci-

dence was significantly lower in pregnant women taking vitamins C and E than in those taking placebo, suggesting vitamin E may be associated with neonatal RDS. Our study showed that cord blood vitamin E levels in the RDS group were lower than in the non-RDS group, but there were no statistical differences in cord blood vitamin E levels or vitamin E deficiency rates across RDS severity levels. Multivariate logistic regression analysis showed that cord blood vitamin E level was not an influencing factor for RDS occurrence, consistent with previous studies [25]. Possible reasons include: (1) Cord blood/serum vitamin E levels may be related to gestational age [28], with significantly lower serum vitamin E levels in preterm infants with RDS at >32 weeks gestational age or >1,500 g birth weight [24]; (2) Alveolar type II epithelial cells take up vitamin E mainly from HDL during PS synthesis and express at least three HDL receptors, the most important being scavenger receptor class B type I (SR-BI), whose expression increases in vitamin E deficiency to enhance vitamin E uptake and increase lung tissue vitamin E concentration. Therefore, cord blood/serum vitamin E levels may not fully reflect lung tissue vitamin E concentration [29].

Notably, vitamins A and E in preterm infants are mainly transported through the maternal placenta, and deficiency in preterm infants may continue maternal deficiency. Jiang Hongqing et al. [30] showed that serum vitamin A levels in pregnant women under routine health care were low in late pregnancy, with vitamin A deficiency incidence of 35.10% and abnormal serum vitamin E levels (mainly overdose) of 15.32%. Therefore, vitamin A supplementation during pregnancy may help reduce preterm RDS incidence, especially severe RDS, and improve prognosis. Although vitamin E is involved in PS synthesis, secreted into alveolar space, and protects PS lipids from oxidation [4,29], and maternal vitamin E supplementation improves fetal lung dysplasia and vascular remodeling [26], fewer studies and human trials have examined the relationship between vitamin E and neonatal RDS. This relationship requires further investigation.

In conclusion, RDS occurrence in preterm infants is related to many factors, with lower cord blood vitamin A and E levels in affected infants. Cord blood vitamin A level is an influencing factor for both RDS occurrence and severity. We recommend vitamin A supplementation during pregnancy to minimize RDS incidence and reduce severity. However, this study had a small sample size and could not examine vitamin A and E levels in mothers, preventing identification of deficiency causes and guidance for supplementation. The relationship between vitamin E and RDS in preterm infants also requires future investigation with larger sample sizes and multicenter research.

Authors' contributions: Liu Weina conceived the research, designed the study protocol, and drafted the manuscript; Liu Weina, Ge Haiyan, and Ma Jing performed data cleaning, statistical processing, and created figures and tables; Ge Haiyan and Ma Jing revised the manuscript; Bai Xingyu and Cui Shifang screened subjects, collected and organized data, and collected specimens; Cao Qinying and Qiao Yanxia were responsible for quality control, revision, and overall supervision of the manuscript.

Conflict of interest: The authors declare no conflict of interest.

References

[1] ZHENG W Y, PAN S L, HUANG Y X, et al. Comparison of maternal risk factors for respiratory distress syndrome in late preterm and term newborns[J]. Guangdong Medical Journal, 2021, 42(7): 773-776. DOI: 10.13820/j.cnki.gdyx.20203127.

[2] FERNANDES-SILVA H, ARAÚJO-SILVA H, CORREIAPINTO J, et al. Retinoic acid: a key regulator of lung development[J]. Biomolecules, 2020, 10(1): 152. DOI: 10.3390/biom10010152.

[3] TIMONEDA J, RODRÍGUEZ-FERNÁNDEZ L, ZARAGOZÁ R, et al. Vitamin A deficiency and the lung[J]. Nutrients, 2018, 10(9): 1132. DOI: 10.3390/nu10091132.

[4] KOLLECK I, SINHA P, RÜSTOW B. Vitamin E as an antioxidant of the lung: mechanisms of vitamin E delivery to alveolar type cells[J]. Am J Respir Crit Care Med, 2002, 166(12 Pt 2): S62-66. DOI: 10.1164/rccm.2206019.

[5] SHAO X M, YE H M, QIU X S. Practical Neonatology[J]. 5th ed. Beijing: People' s Health Publishing House, 2019.

[6] CHEN Z L, LIU J, FENG Z C. Recommended criteria for the diagnosis and classification of neonatal asphyxia[J]. Chinese Journal of Contemporary Pediatrics, 2013, 15(1): 1. DOI: 10.7499/j.issn.1008-8830.2013.01.001.

[7] World Health Organization. Serum retinol concentrations for determining the prevalence of vitamin A deficiency in populations[R]. Geneva: WHO, 2011.

[8] TRABER M G. Vitamin E inadequacy in humans: causes and consequences[J]. Adv Nutr, 2014, 5(5): 503-514. DOI: 10.3945/an.114.006254.

[9] YE W, ZHANG T, SHU Y, et al. The influence factors of neonatal respiratory distress syndrome in Southern China: a case-control study[J]. J Matern Fetal Neonatal Med, 2020, 33(10): 1678-1682. DOI: 10.1080/14767058.2018.1526918.

[10] ZHANG H, SHANG B, TAN Q, et al. Analysis of risk factors of neonatal respiratory distress syndrome and preventive measures[J]. Maternal and Child Health Care of China, 2019, 34(12): 2769-2773. DOI: 10.7620/zgfybj.j.issn.1001-4411.2019.12.34.

[11] LU F Y, CHEN X L, JIANG T H, et al. Clinical analysis of 28 cases of premature delivery combined with neonatal respiratory distress syndrome[J]. China Continuing Medical Education, 2019, 11(24): 83-86. DOI: 10.3969/j.issn.1674-9308.2019.24.035.

[12] CONDÒ V, CIPRIANI S, COLNAGHI M, et al. Neonatal respiratory distress syndrome: are risk factors the same in preterm and term

infants?[J]. J Matern Fetal Neonatal Med, 2017, 30(11): 1267-1272. DOI: 10.1080/14767058.2016.1210597.

[13] OGIHARA T, MINO M. Vitamin E and preterm infants[J]. Free Radic Biol Med, 2022, 180: 13-32. DOI: 10.1016/j.freeradbiomed.2021.11.037.

[14] DING Y, CHEN Z, LU Y. Vitamin A supplementation prevents the bronchopulmonary dysplasia in premature infants: a systematic review and meta-analysis[J]. Medicine (Baltimore), 2021, 100(3): e23101. DOI: 10.1097/MD.0000000000023101.

[15] LIU W, XU P. The association of serum vitamin D level and neonatal respiratory distress syndrome[J]. Ital J Pediatr, 2023, 49(1): 16. DOI: 10.1186/s13052-023-01415-w.

[16] TAO E F, YUAN T M. Biotin A levels and preterm illnesses[J]. Chinese Journal of Contemporary Pediatrics, 2016, 18(2): 177-182. DOI: 10.7499/j.issn.1008-8830.2016.02.015.

[17] MARQUEZ H A, CHEN F. Retinoic acid signaling and development of the respiratory system[J]. Subcell Biochem, 2020, 95: 151-174. DOI: 10.1007/978-3-030-42282-0_6.

[18] BURGOS C M, DAVEY M G, RILEY J S, et al. Lung function and pulmonary artery blood flow following prenatal maternal retinoic acid and imatinib in the nitrofen model of congenital diaphragmatic hernia[J]. J Pediatr Surg, 2018, 53(9): 1681-1687. DOI: 10.1016/j.jpedsurg.2017.12.002.

[19] MADEN M. Retinoids in lung development and regeneration[J]. Curr Top Dev Biol, 2004, 61: 153-189. DOI: 10.1016/S0070-2153(04)61007-6.

[20] MENG J, WU H T. Study on vitamin A and mineral substance in neonatal respiratory distress syndrome[J]. Chinese Journal of Child Health Care, 2015, 23(11): 1221-1223. DOI: 10.11852/zgetbjzz2015-23-11-22.

[21] DAI Y Q, DING L, CHEN Y P, et al. Clinical correlation of vitamin A and neonatal pneumonia, septicemia and respiratory distress syndrome[J]. Contemporary Medicine, 2018, 24(7): 25-27. DOI: 10.3969/j.issn.1009-4393.2018.7.008.

[22] ELFARARGY M S, ABU-RISHA S, AL-ASHMAWY G, et al. Serum vitamin A levels as a novel predictor for respiratory distress syndrome in neonates: is it beneficial?[J]. Endocr Metab Immune Disord Drug Targets, 2022, 22(2): 235-240. DOI: 10.2174/1871530321666210921120258.

[23] JIANG X. Correlation between serum vitamin A level and the severity of neonatal respiratory distress syndrome[J]. Journal of Pediatric Pharmacy, 2017, 23(11): 22-24. DOI: 10.13407/j.cnki.jpp.1672-108X.2017.11.008.

[24] DEGER I, ERTUĞRUL S, YILMAZ S T, et al. The relationship between vitamin A and vitamin E levels and neonatal morbidities[J]. Eur Rev Med Pharmacol Sci, 2022, 26(6): 1963-1969. DOI: 10.26355/eurrev_{{{202203}}_{{28344}}}.

[25] ZHANG Y. Association between serum vitamin A, D and E status and respiratory distress syndrome in preterm infants-a propensity score matching analysis[J]. Turk J Pediatr, 2022, 64(4): 605-611. DOI: 10.24953/turkjped.2021.5011.

[26] LIN H, WANG L H, LIU W Y, et al. Effect of vitamin E on lung development and vascular remodeling in fetal rats with congenital diaphragmatic hernia[J]. Practical Journal of Clinical Medicine, 2012, 9(1): 51-54. DOI: 10.3969/j.issn.1672-6170.2012.01.015.

[27] RUMBOLD A R, CROWTHER C A, HASLAM R R, et al. Vitamins C and E and the risks of preeclampsia and perinatal complications[J]. N Engl J Med, 2006, 354(17): 1796-1806. DOI: 10.1056/NEJMoa054186.

[28] ASSUNÇÃO D G F, SILVA L T P D, CAMARGO J D A S, et al. Vitamin E Levels in preterm and full-term infants: a systematic review[J]. Nutrients, 2022, 14(11): 2257. DOI: 10.3390/nu14112257.

[29] KOLLECK I, WISSEL H, GUTHMANN F, et al. HDL holoparticle uptake by alveolar type cells: effect of vitamin E status[J]. Am J Respir Cell Mol Biol, 2002, 27(1): 57-63. DOI: 10.1165/ajrcmb.27.1.4774.

[30] JIANG H Q, CHEN H, NI J J. Status quo of serum levels of vitamin A and E in pregnancy[J]. Academic Journal of Chinese PLA Medical School, 2015, 36(11): 1118-1121. DOI: 10.3969/j.issn.2095-5227.2015.11.016.

Note: Figure translations are in progress. See original paper for figures.