Vitamin A supplementation prevents the bronchopulmonary dysplasia in premature infants: A systematic review and meta-analysis

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Abstract
Background: It is necessary to evaluate the effectiveness and safety of vitamin A supplementation on the bronchopulmonary dysplasia (BPD) in premature infants.

Methods: Randomized controlled trials (RCTs) on the role of supplemental vitamin A in preterm infants were searched. The Medline et al databases were manually searched from inception to April 30, 2020. Related outcomes including incidence of BPD, retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), sepsis and mortality were assessed with Review Manager 5.3 software, and Random-effect model was applied for all conditions.

Results: A total of 9 RCTs with 1409 patients were included. The analyzed results showed that the incidence of BPD in vitamin A group was significantly less than that of control group (OR = 0.67, 95%CI [0.52-0.88]). There was no significant difference in the incidence of ROP (OR = 0.65, 95%CI [0.29-1.48]), NEC (OR = 0.88, 95%CI [0.59-1.30]), IVH (OR = 0.90, 95%CI [0.65-1.25]), sepsis (OR = 0.84, 95%CI [0.64-1.09]) and mortality (OR = 0.98, 95%CI [0.72-1.34]) among two groups.

Conclusion: Vitamin A supplementation is beneficial to the prophylaxis of BPD in premature infants, further studies on the administration approaches and dosages of vitamin A in premature infants are warranted.

Abbreviations: BPD = bronchopulmonary dysplasia, CI = confidence interval, CNKI = China National Knowledge Infrastructure, IVH = intraventricular hemorrhage, NEC = necrotizing enterocolitis, OR = odd of risk, PRISMA = Preferred Reporting Items for Systematic Review and Meta-Analysis, RCTs = randomized controlled trials, ROP = retinopathy of prematurity.

Keywords: bronchopulmonary dysplasia, infant, premature, vitamin A

1. Introduction
Bronchopulmonary dysplasia (BPD) is one of the most common chronic diseases of premature infants.[1] Not only does the mortality rate are high, but also the impact on surviving children may last for life, bringing a heavy burden on the children’s physical and mental health, family, and society.[2] Moreover, the incidence of BPD is also increasing.[3] Scholars such as Northway first proposed the concept of BPD in 1967.[4] For more than 50 years, humans have conducted a lot of research on the prevention and treatment of BPD. Although many progresses have been made, there is currently no definite and effective treatment, and its prevention is especially important.

Many studies[5,6] have shown that vitamin A may be beneficial for the prevention of BPD. As early as 1987, a double-blind randomized controlled trial (RCT)[7] showed that supplementing vitamin A can reduce the incidence of BPD. However, recently some scholars have proposed the opposite point of view, it is believed that vitamin A is ineffective in preventing BPD and increases the risk of sepsis in children.[7] Tolia et al[8] have also found that the neonatal death and the occurrence of BPD may not be affected by recent vitamin A deficiency. It can be seen that whether vitamin A can prevent the occurrence of BPD is still controversial. Previous meta-analyses[9,10] have compared the effects and safety of vitamin A in the premature infants, yet the results have remained inconsistent. Furthermore, the sample size is rather small. Therefore, an updated meta-analysis on the role of vitamin A in the premature infants is needed. In this present study, we aimed to comprehensively evaluate the effectiveness and safety of supplemental vitamin A in preterm infants, to provide a reference for clinical management of premature infants.

2. Methods
This systematic review and meta-analysis did not pre-registered on the website, and it was reported in following of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.[11]
2.1. Eligibility criteria
Studies were included in this present review if following PICOS criteria were met:
1. Participants: Preterm infants (gestational age <37 weeks) without congenital abnormalities.
2. Intervention: trials that compared patients who received vitamin A vs did not receive vitamin A supplementation.
3. Outcomes: related outcomes on the effects and safety were reported, including the incidence of BPD, retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), sepsis, and mortality.
4. Design: RCT, published in a peer reviewed journal.

The literature exclusion criteria were:
1. The quality of the literature was poor, including serious flaws in research design, improper random methods, etc.
2. For the same study which was published multiple times, the one with the largest sample size was taken, and others were excluded;
3. Unable to obtain the original text or not get sufficient original data for meta-synthesis

Literature search strategy
The Medline, Science Direct, Cochrane Central Register of Controlled Trials, EMBASE, China National Knowledge Infrastructure (CNKI) and Wanfang database were manually searched from inception to April 30, 2020. We used the combination of subject words and free words to perform the search process. The search terms were as follows: (vitamin A OR Vit A OR V A) AND (premature or preterm or neonate or newborn or infant or epilepsy). There were no language restrictions applied during the search process in this present study.

2.3. Data extraction
The two reviewers independently screened the literatures according to the inclusion and exclusion criteria, and used the same data extraction table to extract the data and check with each other. If there were disagreements, they were resolved through discussion or decided by the third researcher. The extracted information included:
1. The first author, the year of publication, the country, and other basic information of the included literature;
2. Research methods and key elements of RCT for the bias risk assessment;
3. interventions, including the time, route, dose, and duration of treatment course;
4. related outcomes: the incidence of BPD, ROP, NEC, IVH, sepsis, and mortality.

The assessment on the quality of included RCTs
The qualities of related RCTs were independently evaluated by two of our reviewers. And any conflicting results were further judged by another author. We used Cochrane Collaboration’s tool of bias risk[12] to assess the methodological quality and potential risk of bias in the included RCTs. This tool includes seven specific domains: sequence generation, assignment hiding, blindness of participants and personnel, blindness of outcome evaluation, incomplete result data, selective result reporting, and other issues. According to the judgment criteria, each domain is classified as low bias risk, high bias risk, or unclear bias risk. Statistical analysis

All the statistical analyses were conducted using the Review Manager 5.3 software (Copenhagen). The odd of risk (OR) with related 95% confidence intervals (CI) was calculated to estimate the synthesized effects of included RCTs. Furthermore, the statistical heterogeneity was evaluated with Q-test and I², and the P values of 25%, 50%, and 75% were taken as being lowly, moderately, and highly heterogeneous respectively. Random-effect model were applied for all conditions. Subgroup analysis based on intervention differences were conducted to ascertain the potential origin of heterogeneity. Furthermore, sensitivity analysis was performed by neglecting one study at one time and evaluating the influence of each included RCTs. For all the statistical analyses in this present meta-analysis, P < .05 was taken as statistical significance, and all examined tests were two-sided.

3. Results

3.1. Study selection
The selection process is presented in Figure 1. The initial search resulted in 161 potentially relevant articles. After reviewing the titles and abstracts of the remaining 104 studies after duplicate exclusion, the full text of 25 studies was retrieved. After careful and discreet evaluation based on the included and excluded criteria, 9 RCTs were included finally.

3.2. The characteristics of included RCTs
A total of 9 RCTs[7,13-20] with 1409 patients were included, of whom 709 infants received vitamin A treatment, and 700 infants did not receive vitamin A treatment. The characteristics of included RCTs were presented in Table 1. Five reported RCTs[7,13,16,18,20] were conducted in the United States, two[14,19] in England, and one in Thailand[17] and China[15] respectively. And dose of vitamin A regimens varied from 1500 to 10,000 IU, and the treatment durations generally lasted for 4 weeks.

3.3. Literature quality evaluation
The quality of included 9 RCTs were presented in Figures 2 and 3. Although each study mentioned randomization, and four RCTs[7,14,16,20] did not mention a specific random method, and there might be pseudo-randomness. Two RCTs[17,20] did not explicitly reported the distribution and concealment or whether to use blind method. One study[120] did not report the type and number of specific adverse reactions in detail, and the remaining four studies all reported that. No other significant biases were detected.

3.4. Synthesized outcomes
The incidence of BPD Six RCTs[7,13,15,16,18,19] reported the incidence of BPD among two groups. No significant heterogeneity was found among included RCTs (I² = 0%). The analysis result showed that the incidence of BPD in the vitamin A group was significantly less than that of control group (OR = 0.67, 95% CI [0.52-0.88], Fig. 4A).

The incidence of ROP Four RCTs[7,13,14,19] reported the incidence of ROP among two groups. No significant heterogeneity was found among included RCTs (I² = 53%). The analysis result showed that there was no significant difference in the incidence of ROP among two groups (OR = 0.65, 95% CI [0.29-1.48], Fig. 4B).
The incidence of NEC Three RCTs\(^{[13,16,18]}\) reported the incidence of NEC among two groups. No significant heterogeneity was found among included RCTs (\(I^2=0\%\)). The analysis result showed that there was no significant difference in the incidence of NEC among two groups (OR = 0.88, 95% CI [0.59–1.30], Fig. 4C).

The incidence of IVH Four RCTs\(^{[13,14,18,19]}\) reported the incidence of IVH among two groups. No significant heterogeneity was found among included RCTs (\(I^2=0\%\)). The analysis result showed that there was no significant difference in the incidence of IVH among two groups (OR = 0.90, 95% CI [0.65–1.25], Fig. 4D).

The incidence of sepsis Three RCTs\(^{[13,18,19]}\) reported the incidence of sepsis among two groups. No significant heterogeneity was found among included RCTs (\(I^2=0\%\)). The analysis result showed that there was no significant difference in the incidence of sepsis among two groups (OR = 0.84, 95% CI [0.64–1.09], Fig. 4E).

Table 1
The characteristics of included RCTs.

| Studies          | Countries | Sample (vit A/control) | Gestational age (w) | Birth weight (g) | Interventions                                      | Frequency and duration |
|------------------|-----------|------------------------|---------------------|------------------|---------------------------------------------------|------------------------|
| Kiatchoosaku 2014 | Thailand  | 40/40                  | 24–32               | <1500             | Vit A group: im, 5000 IU | None                  | 3/w, 4w                |
| Macler 2012      | England   | 42/47                  | <32                 | <1501             | Control group: None                               | 3/w, 2–4w              |
| Pearson 1992     | USA       | 27/22                  | 27 ± 1              | 700–1100          | im, 2000 IU                                      | Normal saline          | Once every other day, a total of 14 times |
| Ravishankar 2003 | USA       | 22/18                  | <32                 | 500–1500          | im, 1500–3000 IU                                 | None                   | The 1st, 3rd, 7th day after birth |
| Shenai 1987      | USA       | 20/20                  | 26–30               | 700–1300          | im, 2000 IU                                      | Normal saline          | Once every other day, a total of 14 times |
| Tyson 1999       | USA       | 405/402                | <30                 | 401–1000          | im, 5000 IU                                      | None                   | 3/w, 4w                |
| Wardle 2001      | England   | 77/77                  | 25–27               | <1000             | po, 2000 IU                                      | Placebo               | 1/4, 28d               |
| Werkman 1994     | USA       | 44/42                  | <31                 | 725–1300          | iv gtt, 210–476 RE                                | None                   | 1/4, 4w                |
| Tang 2016        | China     | 32/32                  | 27–33               | <1500             | po, 5000 IU/kg                                   | None                   | 1/4, 4w                |
The mortality Seven RCTs\(^7,13,15–19\) reported the mortality among two groups. No significant heterogeneity was found among included RCTs \(I^2=0\%\). The analysis result showed that there was no significant difference in the mortality among two groups \((OR=0.98, 95\%CI [0.72–1.34]\), Fig. 4F).

3.5. Sensitivity analysis
The sensitivity analyses were performed by excluding single RCT one by one. The results of sensitivity analysis of all outcomes had indicated no substantial result changes among the overall estimates.

3.6. Publication bias
The publication bias was evaluated with funnel plot. The funnel plots (Fig. 5) for all synthesized outcomes remained symmetrical, indicating that there was no significant publication bias.

4. Discussion
Vitamin A deficiency is a global public health problem\(^21\). Vitamin A is mainly transmitted from the mother through the placenta to the fetus in the third trimester. Therefore, the deficiency vitamin A is prevalent in premature infants\(^22\). Premature birth and low birth weight are important risk factors for BPD\(^23\). The prevalence of BPD in preterm infants with birth weights of 501 to 750g, 1000g, 1250g, and 1500g were 42\%, 25\%, 11\%, and 5\%, respectively\(^24\). Another study\(^25\) has reported that 97\% preterm infants with birth weight \(<1250\)g have BPD. The Canadian Newborn Collaboration\(^26\) reported that the incidence of BPD among surviving infants with a gestational age of \(<25\) weeks was 28.1\%, while the incidence of BPD was only 4\% for infants born with a gestational age of 29 to 32 weeks. Previous studies\(^27,28\) have shown that in the neonates with younger gestational age and the lower birth weight, the vitamin A deficiency is more serious. Meanwhile, BPD is also mainly seen in premature infants with low gestational age\(^29\), suggesting that there may be a relationship between the vitamin A deficiency and BPD. The results of this present meta-analysis have revealed that the vitamin A supplementation can reduce the occurrence of BPD in premature infants, even rough no significant differences on the incidence of ROP, NEC, IVH, sepsis, and mortality were found.
Figure 4. The forest plots for synthesized outcomes.

A. The forest plot for the incidence of BPD

| Study or Subgroup | Weight | Control | Events | Total | Odds Ratio M-H | Random 95% CI |
|-------------------|--------|---------|--------|-------|----------------|---------------|
| Katchacosku 2014  | 4.33   | 0.59    | 0.85   | 0.15  | 6.87 (1.52, 2.88)|               |
| Total             |        |         | 4.43   | 0.85  | 6.87 (1.52, 2.88)|               |

B. The forest plot for the incidence of ROP

| Study or Subgroup | Weight | Control | Events | Total | Odds Ratio M-H | Random 95% CI |
|-------------------|--------|---------|--------|-------|----------------|---------------|
| Katchacosku 2014  | 1.23   | 0.38    | 0.57   | 0.15  | 7.53 (1.52, 2.88)|               |
| Total             |        |         | 1.45   | 0.15  | 7.53 (1.52, 2.88)|               |

C. The forest plot for the incidence of NEC

| Study or Subgroup | Weight | Control | Events | Total | Odds Ratio M-H | Random 95% CI |
|-------------------|--------|---------|--------|-------|----------------|---------------|
| Katchacosku 2014  | 1.45   | 1.45    | 1.45   | 1.45  | 1.45 (1.45, 1.45)|               |
| Total             |        |         | 2.49   | 1.45  | 1.45 (1.45, 1.45)|               |

D. The forest plot for the incidence of IVH

| Study or Subgroup | Weight | Control | Events | Total | Odds Ratio M-H | Random 95% CI |
|-------------------|--------|---------|--------|-------|----------------|---------------|
| Katchacosku 2014  | 1.45   | 1.45    | 1.45   | 1.45  | 1.45 (1.45, 1.45)|               |
| Total             |        |         | 2.49   | 1.45  | 1.45 (1.45, 1.45)|               |

E. The forest plot for the incidence of sepsis

| Study or Subgroup | Weight | Control | Events | Total | Odds Ratio M-H | Random 95% CI |
|-------------------|--------|---------|--------|-------|----------------|---------------|
| Katchacosku 2014  | 1.45   | 1.45    | 1.45   | 1.45  | 1.45 (1.45, 1.45)|               |
| Total             |        |         | 2.49   | 1.45  | 1.45 (1.45, 1.45)|               |

F. The forest plot for the mortality

| Study or Subgroup | Weight | Control | Events | Total | Odds Ratio M-H | Random 95% CI |
|-------------------|--------|---------|--------|-------|----------------|---------------|
| Katchacosku 2014  | 1.45   | 1.45    | 1.45   | 1.45  | 1.45 (1.45, 1.45)|               |
| Total             |        |         | 2.49   | 1.45  | 1.45 (1.45, 1.45)|               |
Previous studies\cite{30,31} have suggested that vitamin A activates SP-B mRNA transcription through the RA-RAR/RXR pathway and tissue-specific thyroid transcription factor (TTF-1) and other factors, increasing SP-B expression. Several reports\cite{32,33} have shown that the lack of vitamin A can cause the content of SP-A, SP-B, and SP-C mRNAs to decrease, and at the same time reduce the expression of fatty acid synthase (FAS) gene, thus affecting the synthesis of phospholipid precursors. Vitamin A may increase phospholipid and lung surfactant protein synthesis through the above two pathways to promote the lung surfactant synthesis, and thus promotes lung development and maturity.\cite{34} In addition, it may be related to the antioxidant protection of vitamin A and the promotion of repair mechanisms after lung injury.\cite{35}

With the use of clinical vitamin A, reports on its adverse reactions have also emerged. The pain and sepsis are the two most commonly see adverse reaction.\cite{36} Therefore, not only the efficacy of vitamin A, but also its safety in premature infants is
worthy of attention and discussion. Previous studies have shown that vitamin A can reduce the incidence of BPD in preterm infants without serious adverse reactions, but Chabra et al have observed an increase in the incidence of infection and sepsis in children receiving vitamin A. The relevant complications of the two groups of patients in the included nine RCTs are not significantly different. This shows that supplementing vitamin A to prevent BPD in preterm infants may be safe, but further verification is still necessary.

Previous experiments in rats have found that vitamin A has a significant effect on lung differentiation and maturition, mainly in the following two aspects. In contrast, lack of vitamin A can cause metaplasia of trachea and bronchial squamous epithelium, and supplementation of vitamin A-related agents can improve its morphological changes. In contrast, vitamin A can affect lung gene expression. Retinyl esters, RBP, and retinoic acid binding proteins can accumulate in the lungs. At the same time, some vitamin A subtypes are expressed in the lungs. The expression of the aforementioned proteins and retinoic acid regulated genes has relevance. If the retinyl ester in the lung is obviously consumed, the cellular RBP level will change significantly, indicating that vitamin A is involved in lung development. Some scholars supplemented the animal model of BPD of premature lambs with vitamin A and have found that it can improve alveolar formation and alveolar capillary growth, reduce the expression of pulmonary parenchymal elastin messenger ribonucleotides and the accumulation of elastic fibers, and achieve better gas exchange. At the same time, some scholars believe that vitamin A deficiency may be one of the reasons for the delayed embryonic lung development in rats by monitoring the levels of related proteins in the rats with absence of fetal lung development. The purpose of this study is to evaluate the effects and safety of BPD by vitamin A. However, the diagnosis can only be made when the oxygen is inhaled 28 days after birth or corrected for gestational age of 36 weeks. Therefore, the focus should also be put on the prevention of BPD.

Several limitations of this present study should be considered. First, the number of high-quality studies on the role of vitamin A in premature infants remains limited, and we failed to conduct subgroup analyses on the results of ROP, future studies with rigorous design are needed. Secondly, the included studies did not observe the long-term neurodevelopment on the painful stimuli caused by repeated intramuscular injections. The longer follow-up periods are needed. Thirdly, the dose of vitamin A in the nine RCTs included in this study varied from 1500 to 10,000 IU, the dose and effect between vitamin A and related outcomes should be further elucidated in the future.

5. Conclusions

In conclusion, vitamin A supplementation is beneficial to reduce BPD in premature infants, and there are no significant differences on the incidence of ROP, NEC, IVH, sepsis, and mortality between two groups. Vitamin A supplementation may be a viable option for the prophylaxis of BPD in premature infants. However, at present, there is still a lack of evidence-based evidence on the administration approaches and dosages of supplementing vitamin A. Limited by the number and quality of included studies, the role of vitamin A in premature infants should be further clarified by more high-quality studies.

Author contributions

Y D designed research; Y D, Z C conducted research; Y D, Y L analyzed data; Y D wrote the first draft of manuscript; Y D had primary responsibility for final content. All authors read and approved the final manuscript.

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References

[1] Tracy MK, Berkelhamer SK. Bronchopulmonary dysplasia and pulmonary outcomes of prematurity. Pediatr Ann 2019;48:e148–53.

[2] González-Luis GE, van Westering-Kroon E, Villamor-Martínez E, et al. Tobacco smoking during pregnancy is associated with increased risk of moderate/severe bronchopulmonary dysplasia: a systematic review and meta-analysis. Front Pediatr 2020;8:160.

[3] Haggie S, Robinson P, Selvadorai H, et al. Bronchopulmonary dysplasia: a review of the pulmonary sequelae in the post-surfactant era. J Paediatr Child Health 2020;56:680–9.

[4] Thebaud B, Krounenhanas S. Can we cure bronchopulmonary dysplasia? J Pediatr 2017;191:12–4.

[5] Jensen EA, Roberts RS, Schmidt B. Drugs to prevent bronchopulmonary dysplasia: effect of baseline risk on the number needed to treat. J Pediatr 2020.

[6] Naeem A, Ahmed I, Silverya P. Bronchopulmonary dysplasia: an update on experimental therapeutics. Eur Med J (Chelmfi) 2019;4:20–9.

[7] Shenai JP, Kennedy KA, Chryl F, et al. Clinical trial of vitamin A supplementation in infants susceptible to bronchopulmonary dysplasia. J Pediatr 1997;111:269–77.

[8] Tolia VN, Murthy K, McKinley PS, et al. The effect of the national shortage of vitamin A on death or chronic lung disease in extremely low-birth-weight infants. JAMA Pediatr 2014;168:1039–44.

[9] Araki S, Kato S, Namba F, et al. Vitamin A to prevent bronchopulmonary dysplasia in extremely low birth weight infants: a systematic review and meta-analysis. PLoS One 2018;13:e0207730.

[10] Struyve L, Thebaud B. Novel therapeutics for bronchopulmonary dysplasia. Curr Opin Pediatr 2018;30:378–83.

[11] Panic N, Leoncini E, de Belvis G, et al. Evaluation of the endorsement of the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement on the quality of published systematic review and meta-analyses. PLoS One 2013;8:e31338.

[12] Jorgensen I, Paludan-Muller AS, Laursen DR, et al. Evaluation of the Cochrane tool for assessing risk of bias in randomized clinical trials: overview of published comments and analysis of user practice in Cochrane and non-Cochrane reviews. Syst Rev 2016;5:80.

[13] Kiatchoosakun P, Jirapraditha J, Panthongviriyakul MC, et al. Vitamin A supplementation for prevention of bronchopulmonary dysplasia in very-low-birth-weight premature Thai infants: a randomized trial. J Med Assoc Thai 2014;97(Suppl 10):S82–88.

[14] Mactier H, McCulloch DL, Hamilton R, et al. Vitamin A supplementation improves retinal function in infants at risk of retinopathy of prematurity. J Pediatr 2012;160:954–9, e951.

[15] Pearson E, Bose C, Snidow T, et al. Trial of vitamin A supplementation in very low birth weight infants at risk for bronchopulmonary dysplasia. J Pediatr 1992;121:420–7.

[16] Ravishankar C, Natiday S, Green RS, et al. A trial of vitamin A therapy to facilitate ductal closure in premature infants. J Pediatr 2003;143:644–8.
[17] Tang J, Li Z, Zou Y, et al. Clinical study on the prevention of neonatal bronchopulmonary dysplasia with high-dose vitamin A. Health Res Prac 2016;36:533–5.

[18] Tyson JE, Wright LL, Oh W, et al. Vitamin A supplementation for extremely-low-birth-weight infants. National Institute of Child Health and Human Development Neonatal Research Network. N Engl J Med 1999;340:1962–8.

[19] Wardle SP, Hughes A, Chen S, et al. Randomised controlled trial of oral vitamin A supplementation in preterm infants to prevent chronic lung disease. Arch Dis Child Fetal Neonatal Ed 2001;84:F9–13.

[20] Werkman SH, Peeples JM, Cooke RJ, et al. Effect of vitamin A supplementation of intravenous lipids on early vitamin A intake and status of premature infants. Am J Clin Nutr 1994;59:586–92.

[21] Timoneda J, Rodriguez-Fernandez L, Zaragoza R, et al. Vitamin A deficiency and the lung. Nutrients 2018;10:

[22] Schwartz E, Zelig R, Parker A, et al. Vitamin A supplementation for the prevention of bronchopulmonary dysplasia in preterm infants: an update. Nutr Clin Pract 2017;32:346–53.

[23] Mactier H. Vitamin A for preterm infants; where are we now? Semin Fetal Neonatal Med 2013;18:166–71.

[24] Kalikkot Thekkeveedu R, Guaman MC, Shivanna B. Bronchopulmonary dysplasia: a review of pathogenesis and pathophysiology. Respir Med 2017;132:170–7.

[25] Bancalari E, Jain D. Bronchopulmonary dysplasia: 50 years after the original description. Neonatology 2019;115:384–91.

[26] Shah PS, Lui K, Sjors G, et al. Neonatal outcomes of very low birth weight infants. Nutr Clin Pract 2013;28:381–8.

[27] Chabra S, Mayock DE, Zerzan J, et al. Vitamin A status after prophylactic intramuscular vitamin A supplementation in extremely low birth weight infants. Nutr Clin Pract 2013;28:381–6.

[28] McGill JL, Kelly SM, Guerra-Maupome M, et al. Vitamin A deficiency impairs the immune response to intranasal vaccination and RSV infection in neonatal calves. Sci Rep 2019;9:13157.

[29] Shen T, Bimali M, Faramawi M, et al. Consumption of vitamin K and vitamin A are associated with reduced risk of developing emphysema. NHANES 2007–2016, Front Nutr 2020;7:47.

[30] Chabra S, Mayock DE, Zerzan J, et al. Vitamin A status after prophylactic intramuscular vitamin A supplementation in extremely low birth weight infants. Nutr Clin Pract 2013;28:381–6.

[31] Gawronski CA, Gawronski KM. Vitamin A supplementation for prevention of bronchopulmonary dysplasia: cornerstone of care or futile therapy? Ann Pharmacother 2016;50:680–4.

[32] Zheng J, He Q, Tang H, et al. Overexpression of miR-455-5p affects retinol (vitamin A) absorption by downregulating STRA6 in a nitrogen-induced CDH with lung hypoplasia rat model. Pediatr Pulmonol 2020;55:1433–9.

[33] Pein H, Kroeberle SC, Voelkel M, et al. Vitamin A regulates Akt signaling through the phospholipid fatty acid composition. FASEB J 2017;31:4566–77.

[34] Kim HJ, Sparrow JR. Bisretinoid phospholipid and vitamin A aldehyde: shining a light. J Lipid Res 2020.

[35] Giridhar S, Kumar J, Attri SV, et al. Intramuscular followed by oral vitamin A supplementation by endotracheal application of a nano-encapsulated preparation is feasible in ventilated preterm lambs. J Aerosol Med Pulm Drug Deliv 2018;31:323–30.

[36] Gryndarh S, Kumar J, Atti SV, et al. Intramuscular followed by oral vitamin A supplementation in neonates with birth weight from 750 to 1250 g: a randomized controlled trial. Indian J Clin Biochem 2020;35:197–204.

[37] Huang J, Zhang L, Tang J, et al. Human milk as a protective factor for bronchopulmonary dysplasia: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed 2019;104:F128–36.