Umbilical cord blood vitamin A levels in relation to the outcome of late-preterm infant: A prospective study

En-Fu Tao
Zhejiang University School of Medicine Children's Hospital
Cai-E Chen
Wenling Maternity and Child Health Care Hospital
Yun-Qin Chen
Wenling Maternity and Child Health Care Hospital
Lin-Yan Cai
Wenling Maternity and Child Health Care Hospital
Tian-Ming Yuan (yuantianming@zju.edu.cn)
Children's Hospital, Zhejiang University School of Medicine

Research article

Keywords: Umbilical cord blood, Vitamin A, Late-preterm infant, Respiratory distress syndrome, Hyperbilirubinemia, Sepsis

Posted Date: December 23rd, 2019

DOI: https://doi.org/10.21203/rs.2.19533/v1

Version of Record: A version of this preprint was published at European Journal of Pediatrics on August 27th, 2020. See the published version at https://doi.org/10.1007/s00431-020-03787-1.

Abstract

Background: Low Vitamin A levels of plasma increase the risk of neonates' morbidity. However, whether umbilical cord blood (UCB) vitamin A levels have an association with the outcomes of late-preterm infants (LPI) is not well established. This study aimed to determine umbilical cord blood vitamin A levels and their correlation with outcomes of late-preterm infants.

Methods: We prospectively studied 208 LPI between January 1, 2014 and June 30, 2015. The specimens of UCB were collected shortly after birth, and vitamin A levels were determined by Enzyme-Linked Immunosorbent Assay. All singleton newborns, with 34+0 weeks to 36+6 weeks' gestational age, were eligible for study inclusion in the studied time intervals. Exclusion criteria included significant congenital malformations or chromosomal abnormality or congenital metabolic disease, or life-threatening disease. All subjects were implemented to follow up, and jaundice, sepsis, respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis, death, etc. were recorded.

Results: The prevalence of low UCB vitamin A level <0.7 μmol/L was 37.5% in LPI. UCB vitamin A levels of LPI with cesarean section was lower than that with vaginal delivery (0.734 (0.634-0.796) μmol/L VS 0.904 (0.666-1.100) μmol/L P = 0.001). Additionally, binary logistic regression analysis revealed that the cesarean section was an independent risk factor for UCB vitamin A level < 0.7 μmol/L. However, UCB vitamin A levels did not correlate with gestational age, birth weight, and sex. Neonates with hospitalization or oxygen supplementation or RDS group had significantly lower UCB vitamin A levels than their counterparties (P < 0.05), other than with hyperbilirubinemia or sepsis (P > 0.05). However, univariate binary logistics regression analysis suggested that UCB vitamin A level < 0.7 μmol/L was not an independent risk factor for hospitalization, oxygen therapy, hyperbilirubinemia, sepsis and RDS.

Conclusions: Low umbilical cord blood vitamin A levels are common among late-preterm infants. Delivery with cesarean section is an independent risk factor for low umbilical cord blood vitamin A level. However, there is no evidence that low vitamin A level is associated with morbidity of late-preterm infants, including hyperbilirubinemia, sepsis and respiratory distress syndrome.

Background

Late-preterm infants (LPI), with gestational age ranging from 34 + 0 to 36 + 6 weeks, have a high prevalence among preterm infants. Although they are near term (gestational age ≧ 37 weeks), LPI has higher morbidity of apnea, respiratory distress, kernicterus [1], and even higher mortality compared with term infants [2, 3]. Accordingly, the pediatrician has the responsibility of caring for them more carefully who may be seemingly healthy but actually at higher risks for morbidities.

Vitamin A, a kind of fat-soluble vitamin, has many physiological functions. It plays an essential role in the promotion of growth and differentiation of retina and the lung. Vitamin A is also involved in maintaining epithelial integrity, bone development and immunity [4]. Additionally, Vitamin A may promote the maturation of type II alveolar epithelial cells [5]. However, abnormal Vitamin A is associated with many

diseases, such as night blindness, dry eye, corneal softening, corneal ulcers, immune dysfunction, respiratory infections, etc. A large body of evidence showed that insufficient Vitamin A was closely related to the morbidity of premature infants. If vitamin A deficiency occurs during pregnancy, the pulmonary surfactant will be poorly produced with reduced phospholipid and protein content [5], and thus prone to develop respiratory distress syndrome (RDS). One study indicated that serum retinol (potent vitamin A) insufficient was associated with an increased risk for severe RDS and adverse pulmonary outcome, such as bronchopulmonary dysplasia (BPD) in preterm infants < 1250 g or < 29 weeks' gestation [6]. Esteban-Pretel suggested that vitamin A deficiency can adversely affect the alveolar function and increase the risk of lung disease [7].

Moreover, preterm neonates born with low vitamin A levels have an increased risk of developing chronic lung disease [8]. Besides, preterm infants are susceptible to develop hyperbilirubinemia. That is partly because low vitamin A concentration increases oxidative damage to red cell membranes driven from oxidative stress [9].

Additionally, vitamin A deficiency could reduce both cellular and humoral immunity in the intestinal mucosa [10]. Vitamin A deficiency increases the permeability of the gut. But this harmful effect can be improved with Vitamin A supplementation [11]. Likewise, vitamin A supplementation ameliorates butyric acid-induced intestinal mucosal injury in newborn rats [12]. In addition, the supplementation of trans-retinoic acid (a kind of Vitamin A complex) mitigated intestinal impairment in a rat model of necrotizing enterocolitis (NEC) [13]. Furthermore, Xiao S et al. complicated that vitamin A may regulate intestinal flora, alleviate inflammatory reactions, and enhance the intestinal epithelial barrier in NEC [14].

The umbilical cord connects fetus and placenta and helps the exchange of waste and nutrients between the fetus and mother. Therefore, changes in the composition of cord blood may reflect a specific disease state of the newborns. Meanwhile, samples obtained from UCB are easier than peripheral vascular. Also, puncture of the umbilical cord will not cause adverse effects on the newborns. Based on the above advantages of UCB, some studies investigated biomarkers of UCB for predicting neonatal diseases [15, 16].

Previous researches demonstrated that insufficient serum Vitamin A levels increased the risk for RDS and adverse pulmonary outcome of very low birth weight infants [6, 17]. However, seldom study investigated how vitamin A levels affect LPI' morbidity. Based on the mentioned above, we hypothesized that low UCB vitamin A level may increase the morbidity of the LPI. Accordingly, we conducted a prospective study. First, we collected specimens of UCB to determine vitamin A levels. Second, to follow-up subsequent neonatal morbidity. Third, to investigate the relationship between UCB vitamin A levels and outcomes of LPI. Finally, to clarify the value of UCB vitamin A levels for predicting the morbidity of LPI. If that, it may help pediatrician to take better care of at-risk LPI.

Methods

We conducted a prospective study between January 1, 2014, and June 30, 2015, in Wenlin Maternity and Child Health Care Hospital. All singleton LPI were eligible for the study. Newborns who had significant congenital malformations or chromosomal abnormality or congenital metabolic disease, or life-threatening disease were excluded. The survey collected 210 umbilical cord blood samples, exclusion of 2 specimens due to insufficient umbilical cord blood samples; it ultimately enrolled 208 cases.

Obstetricians or midwives picked umbilical blood samples of 3ml from the maternal end of the umbilical cord vein after umbilical cords were clamped and cut in the delivery room or operating room. The collected samples were injected into the anticoagulant brown tube. To avoid light preservation, centrifugal extraction of supernatant, -20℃ cryopreservation, for subsequent detection. Vitamin A levels were determined using Enzyme-Linked Immunosorbent Assay (ELISA). Implement Vitamin A testing when accumulating to 90 samples. The accomplished test required a total of 6 kits of vitamin A (96T). The reagent box was used to determine the level of human vitamin A in the specimen by double antibody sandwich method. The purified human vitamin antibody package was made into a microporous plate to make solid-phase antibodies. Adding vitamin A to the microporous pores, and then combining with horseradish peroxidase (HRP) labelled Vitamin A antibodies to form an antibody-antigen-enzyme labelled antibody complex, after thorough washing then adding substrate 3,3',5,5'-tetramethylbenzidine (TMB) colour. Transforming TMB into blue under the catalysis of the HRP and converting into the final yellow under the action of acid. The shades of colour positively correlated with vitamin A in the sample. The absorbance (OD value) was determined at 450nm wavelength by enzyme marker, and the standard curve calculated the concentration of the vitamin A in the sample.

All subjects were implemented to follow up, and the following conditions were recorded: jaundice, sepsis, RDS, BPD, NEC, death, etc. Pediatricians of the neonatal department with extensive clinical experience conducted daily check-ups of obstetric newborns. Those suffering from neonatal diseases were admitted to the Department of Neonatology for treatment until they discharged from the hospital. Those without abnormalities were also followed up until discharge together with their mother.

Definitions

Bilirubin levels were interpreted according to the infant's age in hours. Hyperbilirubinemia was defined as serum bilirubin levels exceeding the 95th percentile high-risk zone or total serum bilirubin increasing by more than 5 mg/dL every 24 hours [18, 19]. Oxygen supplementation refers to various forms of respiratory support, including mechanical ventilation, continuous positive airway pressure (CPAP), bi-level positive airway pressure (BiPAP), head net, and nasal catheter. Sepsis was defined as a systemic inflammatory response in the presence of or as a result of a suspected or proven infection [20]. RDS was determined based on the classic signs of respiratory distress as well as the exclusion of other causes of respiratory failure. The diagnosis of RDS was confirmed radiologically in cases of reduced lung volume, reticulogranular lung consolidation, and air bronchograms [21]. BPD was identified when there was clinical evidence of BPD combined with the requirement of oxygen therapy at 28 days of life [22]. NEC was clinically and radiographically diagnosed using the modified Bell's criteria [23]. UCB vitamin A level

was divided into two range, low vitamin A level < 0.70 μmol/L and vitamin A level ≥ 0.7 μmol/L as used in other studies [6].

Statistical methods

Normally distributed data were expressed as the mean ± standard deviation. Continuous variables were compared between 2 groups using the Student's *t*-test. Non-normally distributed data were expressed as medians (interquartile range), and data were compared between 2 groups using the Mann-Whitney *U* test. Countable data were expressed as a number (%). Data were compared between groups using the chi-square or Fisher's exact test. Association analysis was carried out with Pearson association analysis or Spearman rank association analysis according to the distribution. Univariate and binary logistic regression models were used to investigate whether risk factors were independently associated with outcome variables. Results were described as odds ratios (*OR*) and 95% confidence intervals (*CL*). *P*-value < 0.05 were considered statistically significant. All data were analysed by IBM Statistical Package for the Social Sciences (SPSS), version 23 (IBM Corporation).

Results

Clinical characteristics of LPI

The study cohort comprised 208 LPI from 2014 to 2015. The clinical characteristics and outcomes of the study population were summarized in Table 1. Of the 208 subjects, 112 (53.8%)were boys, and 96 (46.2%) were girls. A total of 123 (59.1%) infants were delivered by vaginal while 85 (40.9%) were delivered by cesarean section. Only two (1%) infants had low 1 min Apgar score, with 5 and 7 respectively. The median of UCB vitamin A level in LPI was 0.754 (0.656, 0.892) μmol/L. The prevalence of low UCB vitamin A level <0.7 μmol/L was 37.5% (78/208).

Potential factors affecting UCB vitamin A levels

We analysed various potential factors that may affect UCB vitamin A levels, such as gestational age, birth weight, 1 min Apgar score, 5 min Apgar score, delivery mode, and also sex (Fig 1). We found that UCB vitamin A levels had positive significantly correlation with gestational age and birth weight, with $r = 0.168$ $P = 0.0151$ and $r = 0.168$ $P = 0.0151$ respectively (Fig 1. a, b). However there was no significant correlation with UCB vitamin A levels and 1, 5 min Apgar score (Fig 1. c, d). Concerning delivery mode, UCB vitamin A level of LPI with vaginal delivery was higher than that with cesarean section (0.904 (0.666-1.100) μmol/L VS 0.734 (0.634 -0.796) μmol/L, $P = 0.001$) (Fig 1. e). In contrast, there was no significant difference of UCB vitamin A levels between male and female (0.848 (0.656-0.976) μmol/L VS 0.819(0.639-0.867) μmol/L, $P = 0.431$) (Fig 1. f). Binary logistic regression analysis showed that compared with vaginal delivery, cesarean section was an independent risk factor for UCB vitamin A level < 0.7 μmol/L (*OR* = 6.032 95% *CI* 2.116-18.774, $P = 0.001$). However, gestational age, birth weight and sex were not the independent risk factor for UCB vitamin A level < 0.7 μmol/L in LPI. These data were shown in Table 2.

Comparison of UCB vitamin A levels in LPI with different outcomes

We compared different UCB vitamin A levels of various outcomes of LPI (Table 3). We observed that UCB vitamin A levels of hospitalization proup was lower than that of non-hospitalization proup (0.718 (0.662, 0.945 μmol/L) vs (0.767 (0.660, 0.960) μmol/L, Z = -2.016, P = 0.044). Besides, UCB vitamin A levels of oxygen supplementation group was lower than that of non-oxygen supplementation group (0.699 (0.592, 0.815) μmol/L vs 0.767 (0.663, 0.928) μmol/L, Z = -2.312, P = 0.021). Furthermore UCB vitamin A levels of RDS group was lower than that of non-RDS grouo (0.678 (0.572, 0.780) vs 0.766 (0.659, 0.929), Z = -2.401, P = 0.016). However, there was no significant difference not only between UCB vitamin A levels with or without hyperbilirubinemia group, but also between with or without sepsis group (Z = -0.19, P = 0.99 and Z = -1.183, P =0.237 respectively) .

UCB vitamin A levels in relation to outcomes of LPI

Spearman correlation analysis indicated that UCB vitamin A level had a weak significantly negtive correlation with hospitalization（r = -0.140, P = 0.043 ）, oxygen supplementation (r = -0.161, P = 0.020), and RDS (r= -0.167, P = 0.016) (Table 4). By contrast, there was no significant correlation between UCB vitamin A levels and hyperbilirubinemia (r = -0.001, P = 0.985), as well as sepsis (r = -0.082, P = 0.238) (Table 4). Comparison of the incidence of outcomes in LPI with UCB vitamin A level <0.7 μmol/L or ≥ 0.7 μmol/L were displayed in Fig 2. There were no significant different prevalences of hospitalization, oxygen supplementation, hyperbilirubinemia, sepsis as well as RDS between low UCB vitamin A level < 0.7 μmol/L group and UCB vitamin A level ≥ 0.7 μmol/L group, all of P >0.05). Also, univariate binary logistics regression analysis suggested that UCB vitamin A level < 0.7μmol/L was not a influence factor for 1 min Apgar score ≤ 7 (OR = 0.000, 95% CI (0.000-), P = 0.997), 5 min Apgar score ≤ 7 (OR -,95% CI (--)), hospitalization (OR = 1.368, 95% CI (0.719-2.603), P = 0.339), oxygen supplementation (OR = 1.839, 95% CI (0.861-3.927), P = 0.116), hyperbilirubinemia (OR = 0.819, 95% CI (0.420-1.596), P = 0.558), sepsis (OR = 2.158, 95% CI (0.562-8.289), P = 0.263), as well as RDS (OR = 2.444, 95% CI (0.979-6.102), P = 0.055) . These results were showed in Table 5.

Discussion

In the present prospective study, we determined UCB vitamin A levels and investigated their relationship with outcomes of LPI. We observed that the median of UCB vitamin A level of LPI was 0.754 (0.656, 0.892) μmol/L (Table 1), a bit higher than previous research [24], in which the UCB vitamin A level was 0.55 ± 0.17 μmol/L. However, that study did not mention the birth weight of LPI. Another research suggests that UCB vitamin A levels less than 1.05 μmol/L were measured in 22/56, and levels below 0.7 μmol/L only in 2/56 for gestational age < 33 weeks [8]. These results were inconsistent. One probable reason was the different gestational age and birth weight involved in the studies. Nevertheless, preterm infants are prone to low vitamin A level [24]. Our result revealed that the prevalence of low UCB vitamin A levels < 0.7 μmol/L in LPI was high with 37.5% (78/208). The potential reasons for this are as follows. Firstly, fetuses themselves cannot synthesize vitamin A. They depended on the maternal placental supply

primarily in late pregnancy [25]. Secondly, retinol-binding protein (RBP) manufactured in the fetal liver during the final quarter of pregnancy played a vital role in fetal vitamin A transportation. Additionally, premature infants failed to synthesize enough RBP to transport vitamin A [26, 27]. Thus newborns born with preterm are more likely to have low vitamin A level.

We compared the effects of various factors on vitamin A levels, including gestational age, birth weight, 1 min Apgar score, 5 min Apgar score, delivery mode as well as sex. Interestingly, we found that UCB vitamin A level of LPI with cesarean section was significantly lower than that with vaginal delivery (0.734 (0.634–0.796) μmol/L VS 0.904 (0.666-1.100), P = 0.001) (Fig. 1. e). Besides, binary logistic regression analysis indicated that the cesarean section was an independent factor for low UCB vitamin A level < 0.7 μmol/L. That can be explained that vaginal deliveries without anaesthesia were more stressful events than cesarean deliveries, and this stress was associated with an increase in maternal corticosteroids [28]. Finally, corticosteroids increased placental cord concentrations of vitamin A [29]. Thus, LPI with cesarean deliveries had relative lower UCB vitamin A level. However, Gonzalez-Corbella MJ et al. reported that there was no significant difference in vitamin A levels between vaginal and cesarean deliveries [29]. This inconsistent result may be attributable to fewer subjects (35 vaginal and 21 cesarean deliveries) in the study. Therefore, we still firmly believe that UCB vitamin A levels are significantly lower with cesarean section than vaginal delivery. Additionally, our result indicated that vitamin A levels in our study were not correlated with birth weight, gestational age and also sex in LPI. These results were consistent with previous research [8, 29].

Vitamin A may act on the lung's retinoic acid receptors to up-regulate the transcription and expression of the surfactant protein-B gene and, as a result, promote the synthesis of pulmonary surfactant [30]. Besides, mild vitamin A deficiency has been shown to delay fetal lung maturation in rats. The amounts of surfactant protein-A, B, and C messenger RNAs were decreased by 46%, 32%, and 28%, respectively, in vitamin A deficient fetuses [5]. Kiatchoosakun P et al. suggested that supplementation with vitamin A can reduce the time of intubation and oxygen supplementation and shorten the length of a hospital stay [31]. However, another research reported no difference in the duration of oxygen therapy between a vitamin A supplementation group and a control group [32]. In parallel, our founding showed that vitamin A level < 0.7 μmol/L was not an independent risk factor for hospitalization, oxygen supplementation and RDS in PLI (Table 5). Our founding agreed with the previous study [8]. Our evidence may infer that although vitamin A can promote lung surfactant synthesis, and thus promote lung maturation. But this merit may not have a significant effect on late preterm infants who have relatively mature lungs compared with other preterm infants. Of course, it needs further study.

Vitamin A can regulate non-specific and specific immunity and protect against bacterial infection as an antioxidant [33]. Shenai et al. demonstrated that plasma vitamin A concentrations decreased during airway infection in premature neonates [34]. However, the results of the present study showed that the prevalence of sepsis in LPI between UCB vitamin A level < 0.7 μmol/L and ≧ 0.7 μmol/L had no significant difference. UCB vitamin A level < 0.7 μmol/L was not an independent risk factor for sepsis (Table 5).

Additionally, we found that there was no significant difference in the prevalence of hyperbilirubinemia with different vitamin A levels. UCB vitamin A level < 0.7 was not an independent risk factor for hyperbilirubinemia in LPI. To our knowledge, there is limited published literature reporting an association between vitamin A concentrations and hyperbilirubinemia in LPI. Therefore, this theory requires a larger sample based on specific population to verify. In the present study, none of the neonates suffered from BPD, NEC, and death. Thus, the relationship between UCB vitamin A levels and BPD, NEC or death in LPI requires further study.

Our study should be interpreted with limitations in mind. First, the number of subjects involved in this study is small, although this is one of the extensive survey reported in the literature. Besides, due to limited funds, we did not measure other vitamins or micronutrients, which possibly impacted on the results.

Conclusions

Low umbilical cord blood vitamin A levels are common among late-preterm infants. Delivery with cesarean section is an independent risk factor for low umbilical cord blood vitamin A level. However, there is no evidence that low vitamin A level is associated with morbidity of late-preterm infants, including hyperbilirubinemia, sepsis and respiratory distress syndrome.

Abbreviations

LPI: Late-preterm infants; RDS: respiratory distress syndrome; BPD: bronchopulmonary dysplasia; NEC: necrotizing enterocolitis; UCB: umbilical cord blood; ELISA: Enzyme-Linked Immunosorbent Assay; HRP: horseradish peroxidase; TMB: 3,3',5,5'-Tetramethylbenzidine; CPAP: continuous positive airway pressure; BiPAP: bi-level positive airway pressure; OR: odds ratio; CI: confidence interval; RBP: retinol-binding protein.

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the medical ethical committee of Wenling Maternity and Child Health Care Hospital (approval no. 2018-01218). Written informed consent was obtained from the mother or legal guardian of each neonate before inclusion into this study. A copy of the consent forms is available upon request.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

Funding

The work of the authors was supported by grants from the National Natural Science Foundation of China (81571466), the Zhejiang Provincial Program for the Cultivation of High-level Innovative Health Talents and the Science and Technology Foundation of Taizhou City, Zhejiang Province, China (1902ky159).

Authors' contributions

Conceptualization and methodology: Tian-Ming Yuan. Collection and recording of specimens Cai-E Chen, Lin-Yan Cai. Follow up and management of late-preterm infants: Cai-E Chen, Yun-Qin Chen, En-Fu Tao. Analysis, writing, original draft preparation: En-Fu Tao. Writing - review and editing: Tian-Ming Yuan. All authors read and approved the final manuscript.

Acknowledgements

Not applicable

Authors' information

[1]Department of Neonatology, Children’ s Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang Province, People’ s Republic of China.

[2]Wenling Maternity and Child Health Care Hospital, Wenling, Taizhou, Zhejiang Province, People’ s Republic of China.

References

1. Raju TN, Higgins RD, Stark AR, Leveno KJ. Optimizing care and outcome for late-preterm (near-term) infants: a summary of the workshop sponsored by the National Institute of Child Health and Human Development. Pediatrics. 2006;118(3):1207-1214.
2. Gill JV, Boyle EM. Outcomes of infants born near term. Arch Dis Child. 2017; 102(2):194-198.
3. Kramer MS, Demissie K, Yang H, Platt RW, Sauve R, Liston R. The contribution of mild and moderate preterm birth to infant mortality. Fetal and Infant Health Study Group of the Canadian Perinatal Surveillance System. JAMA. 2000;284(7):843-849.
4. Mactier H. Vitamin A for preterm infants; where are we now? Semin Fetal Neonatal Med. 2013;18(3):166-171.

5. Chailley-Heu B, Chelly N, Lelievre-Pegorier M, Barlier-Mur AM, Merlet-Benichou C, Bourbon JR. Mild vitamin A deficiency delays fetal lung maturation in the rat. Am J Respir Cell Mol Biol. 1999;21(1):89-96.
6. Chen HJ, Hsu CH, Chiang BL. Serum retinol levels and neonatal outcomes in preterm infants. J Formos Med Assoc. 2017;116(8):626-633.
7. Esteban-Pretel G, Marin MP, Renau-Piqueras J, Barber T, Timoneda J. Vitamin A deficiency alters rat lung alveolar basement membrane: reversibility by retinoic acid. J Nutr Biochem. 2010;21(3):227-236.
8. Tammela O, Aitola M, Ikonen S. Cord blood concentrations of vitamin A in preterm infants. Early Hum Dev. 1999;56(1):39-47.
9. Turgut M, Basaran O, Cekmen M, Karatas F, Kurt A, Aygun AD. Oxidant and antioxidant levels in preterm newborns with idiopathic hyperbilirubinaemia. J Paediatr Child Health. 2004;40(11):633-637.
10. Yang Y, Yuan Y, Tao Y, Wang W. Effects of vitamin A deficiency on mucosal immunity and response to intestinal infection in rats. Nutrition. 2011;27(2):227-232.
11. Turfkruyer M, Rekima A, Macchiaverni P, Le Bourhis L, Muncan V, van den Brink GR et al. Oral tolerance is inefficient in neonatal mice due to a physiological vitamin A deficiency. Mucosal Immunol. 2016;9(2):479-491.
12. Nafday SM, Green RS, Chauvin SN, Holzman IR, Magid MS, Lin J. Vitamin A supplementation ameliorates butyric acid-induced intestinal mucosal injury in newborn rats. J Perinat Med. 2002;30(2):121-127.
13. Ozdemir R, Yurttutan S, Sari FN, Oncel MY, Erdeve O, Unverdi HG et al. All-trans-retinoic acid attenuates intestinal injury in a neonatal rat model of necrotizing enterocolitis. Neonatology. 2013;104(1):22-27.
14. Xiao S, Li Q, Hu K, He Y, Ai Q, Hu L et al. Vitamin A and Retinoic Acid Exhibit Protective Effects on Necrotizing Enterocolitis by Regulating Intestinal Flora and Enhancing the Intestinal Epithelial Barrier. Arch Med Res. 2018;49(1):1-9.
15. Mazouri A, Fallah R, Saboute M, Taherifard P, Dehghan M. The prognostic value of the level of lactate in umbilical cord blood in predicting complications of neonates with meconium aspiration syndrome. J Matern Fetal Neonatal Med. 2019;1-7.
16. Castillo A, Grogan TR, Wegrzyn GH, Ly KV, Walker VP, Calkins KL. Umbilical cord blood bilirubins, gestational age, and maternal race predict neonatal hyperbilirubinemia. PLoS One. 2018;13(6):e0197888.
17. Inder TE, Graham PJ, Winterbourn CC, Austin NC, Darlow BA. Plasma vitamin A levels in the very low birthweight infant--relationship to respiratory outcome. Early Hum Dev. 1998;52(2):155-168.
18. American Academy of Pediatrics Subcommittee on H. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2004;114(1):297-316.
19. Dennery PA, Seidman DS, Stevenson DK. Neonatal hyperbilirubinemia. N Engl J Med. 2001;344(8):581-590.

20. Goldstein B, Giroir B, Randolph A, International Consensus Conference on Pediatric S. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med. 2005;6(1):2-8.
21. Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Plavka R et al. European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants–2013 update. Neonatology. 2013;103(4):353-368.
22. Ehrenkranz RA, Walsh MC, Vohr BR, Jobe AH, Wright LL, Fanaroff AA et al. Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. Pediatrics. 2005;116(6):1353-1360.
23. Zecca E, de Luca D, Costa S, Marras M, de Turris P, Romagnoli C. Delivery room strategies and outcomes in preterm infants with gestational age 24-28 weeks. J Matern Fetal Neonatal Med. 2006;19(9):569-574.
24. Galinier A, Periquet B, Lambert W, Garcia J, Assouline C, Rolland M et al. Reference range for micronutrients and nutritional marker proteins in cord blood of neonates appropriated for gestational ages. Early Hum Dev. 2005;81(7):583-593.
25. Agarwal K, Dabke AT, Phuljhele NL, Khandwal OP. Factors affecting serum vitamin A levels in matched maternal-cord pairs. Indian J Pediatr. 2008; 75(5):443-446.
26. Werkman SH, Peeples JM, Cooke RJ, Tolley EA, Carlson SE. Effect of vitamin A supplementation of intravenous lipids on early vitamin A intake and status of premature infants. Am J Clin Nutr. 1994;59(3):586-592.
27. Mactier H, Weaver LT. Vitamin A and preterm infants: what we know, what we don't know, and what we need to know. Arch Dis Child Fetal Neonatal Ed 2005;90(2):F103-108.
28. Quadro L, Hamberger L, Gottesman ME, Wang F, Colantuoni V, Blaner WS et al. Pathways of vitamin A delivery to the embryo: insights from a new tunable model of embryonic vitamin A deficiency. Endocrinology. 2005; 146(10):4479-4490.
29. Gonzalez-Corbella MJ, Lopez-Sabater MC, Castellote-Bargallo AI, Campoy-Folgoso C, Rivero-Urgell M. Influence of caesarean delivery and maternal factors on fat-soluble vitamins in blood from cord and neonates. Early Hum Dev 1998;53 Suppl:S121-134.
30. Yan C, Naltner A, Martin M, Naltner M, Fangman JM, Gurel O. Transcriptional stimulation of the surfactant protein B gene by STAT3 in respiratory epithelial cells. J Biol Chem. 2002;277(13):10967-10972.
31. Kiatchoosakun P, Jirapradittha J, Panthongviriyakul MC, Khampitak T, Yongvanit P, Boonsiri P. 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.
32. Uberos J, Miras-Baldo M, Jerez-Calero A, Narbona-Lopez E. Effectiveness of vitamin A in the prevention of complications of prematurity. Pediatr Neonatol. 2014;55(5):358-362.
33. Ross AC, Chen Q, Ma Y. Vitamin A and retinoic acid in the regulation of B-cell development and antibody production. Vitam Horm. 2011;86:103-126.

34. Shenai JP, Chytil F, Parker RA, Stahlman MT. Vitamin A status and airway infection in mechanically ventilated very-low-birth-weight neonates. Pediatr Pulmonol. 1995;19(5):256-261.

Tables

Table 1. Clinical characteristics and outcomes of late-preterm infants

Features	Late preterm infants, n = 208
Sex（male：female）	112 / 96
Gestational age (Weeks)	35.68 ± 0.74
Birth weight（g）	2613.32 ± 425.57
Mode of delivery （Vaginal ：Cesarean section）	123 / 85
1 min Apgar score ≤ 7	2（1%）
5 min Apgar score ≤ 7	0（0）
UCB vitamin A level (<0.7 μmol/L: ≥ 0.7 μmol/L)	78 / 130
Hospitalization	51 (24.5%)
Oxygen supplementation	32 (15.4%)
Hyperbilirubinemia	50 (24%)
Sepsis	9 (4.3%)
RDS	21 (10.1%)
BPD	0 (0)
NEC	0 (0)
Death	0 (0)

Abbreviations: UCB umbilical cord blood, RDS respiratory distress syndrome, BPD bronchopulmonary dysplasia, NEC necrotizing enterocolitis

Table 2. Potential factors associated with UCB vitamin A level < 0.7 μmol/L in late-preterm infants

Factors	OR (95% CI)	P
Male	0.676 (0.305-1.496)	0.333
Female	1.480（0.669-3.276）	0.333
Gestational age	1.067 (0.589-1.935)	0.830
Birth weight	1.001（0.999-1.002）	0.332
Vaginal delivery	0.159 (0.053-0.473）	0.001
Cesarean section	6.302（2.116-18.774）	0.001

Data were analyzed by binary logistic regression

Abbreviations: UCB umbilical cord blood, RDS respiratory distress syndrome, OR odds ratio, CI confidence interval

Table 3. Comparison of UCB vitamin A levels in late-preterm infants with different outcomes

Outcome	N, (%)	UCB vitamin A level （μmol/L） median (P25, P75)	*Z*	*P*- value
Hospitalization	51 (24.5%)	0.767 (0.660, 0.960)	-2.016	0.044*
Non-hospitalization	157 (75.5)	0.718 (0.662, 0.945)		
Oxygen supplementation	32 (15.4%)	0.699 (0.592, 0.815)	-2.312	0.021*
Non-oxygen supplementation	176 (84.6)	0.767 (0.663, 0.928)		
Hyperbilirubinemia	50 (24%)	0.752 (0.656, 0.897)	-0.19	0.99
Non-hyperbilirubinemia	158 (76%)	0.757 (0.651, 0.899)		
Sepsis	9 (4.3%)	0.692 (0.564, 0.915)	-1.183	0.237
Non-sepsis	199 (95.7%)	0.759 (0.658, 0.893)		
RDS	21 (10.1%)	0.678 (0.572, 0.780)	-2.401	0.016*
Non-RDS	187 (89.9)	0.766 (0.659, 0.929)		
BPD	0 (0)	-	-	-
NEC	0 (0)	-	-	-
Death	0 (0)	-	-	-

Abbreviations: UCB umbilical cord blood, RDS respiratory distress syndrome, BPD bronchopulmonary dysplasia, NEC necrotizing enterocolitis, *$P < 0.05$

Table 4. Correlation of UCB vitamin A level and hospitalization, oxygen supplementation, hyperbilirubinemia, sepsis, and RDS

Statistical index	Hospitalization	Oxygen therapy	Hyperbilirubinemia	Sepsis	RDS
r	-0.140	-0.161	-0.001	-0.082	-0.167
P-value	0.043*	0.020*	0.985	0.238	0.016*

Data were analyzed by Spearman rank association analysis

Abbreviations: UCB umbilical cord blood, RDS respiratory distress syndrome, *$P < 0.05$

Table 5. Effect of UCB vitamin A level < 0.7 μmol/L for outcomes in late-preterm infants

Outcomes	*OR* (95% *CI*)	*P*
1 min Apgar score ≤ 7	0.000 (0.000-)	0.997
5 min Apgar score ≤ 7	-	-
Hospitalization	1.368 （0.719-2.603）	0.339
Oxygen supplementation	1.839 （0.861-3.927）	0.116
Hyperbilirubinemia	0.819（0.420-1.596）	0.558
Sepsis	2.158 （0.562-8.289）	0.263
RDS	2.444 （0.979-6.102）	0.055

Data were analyzed by univariate binary logistics regression analysis

Abbreviations: UCB umbilical cord blood, RDS respiratory distress syndrome, *OR* odds ratio, *CI* confidence interval

Figures

Figure 1

Potential factors affecting UCB vitamin A levels. UCB vitamin A levels had positive significantly correlation with gestational age and birth weight, with r =0.168 P = 0.0151 and r =0.168 P = 0.0151 respectively (Fig 1. a, b). There was no significant correlation with UCB vitamin A levels and 1, 5 min Apgar score (Fig 1. c, d). UCB vitamin A level of LPI with cesarean section was lower than that with vaginal delivery (0.734 (0.634-0.796) μmol/L VS 0.904 (0.666-1.100) μmol/L, P = 0.001) (Fig 1. e). There was no significant difference of UCB vitamin A levels between male and female (0.848(0.656-0.976) μmol/L VS 0.819(0.639-0.867) μmol/L, P = 0.431) (Fig 1. f). *P < 0.05

Figure 2

Various UCB vitamin A levels and outcomes of late-preterm infants. There were no significant different prevalences of hospitalization, oxygen therapy, hyperbilirubinemia, sepsis as well as RDS between low UCB vitamin A level < 0.7 μmol/L and UCB vitamin A level ≥ 0.7 μmol/L, all of P > 0.05).