The relationship between umbilical cord blood vitamin A levels and late preterm infant morbidities: A prospective cohort study

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Abstract

Background: Low plasma vitamin A levels increases the risk of neonates' morbidity. However, the relationship between umbilical cord blood (UCB) vitamin A levels and late-preterm infant (LPI) consequences is inconclusive. Herein, we attempted to clarify the association between UCB vitamin A levels and LPI morbidities.

Methods: We conducted a prospective cohort study of 208 LPI (from 34+0 to 36+6 weeks gestational age) between January 1, 2014 and June 30, 2015. UCB specimens were collected shortly after birth, and vitamin A levels were determined by enzyme-linked immunosorbent assay. Jaundice, sepsis, respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis, and death were recorded.

Results: Prevalence of low UCB vitamin A level <0.7 μmol/L was 37.5% in LPI. Cesarean section was an independent risk factor of UCB vitamin A level < 0.7 μmol/L. Nevertheless, UCB vitamin A levels did not correlate with gestational age, birthweight, and gender. UCB vitamin A level < 0.7 μmol/L was not an independent risk factor for hospitalization, oxygen supplementation, hyperbilirubinemia, sepsis and respiratory distress syndrome. However, cesarean section, gestational age < 35 weeks and birthweight < 2500 g were independent risk factors for hospitalization and RDS. In addition, cesarean section increased the risk of oxygen supplementation, while gestational age < 35 weeks increased the risk of hyperbilirubinemia.

Conclusions: Cesarean section delivery is an independent risk factor of low UCB vitamin A levels, and increases the risk of RDS. On the basis of our results, there is no association between low vitamin A levels and morbidity of late-preterm infants, including hyperbilirubinemia, sepsis and respiratory distress syndrome.

Trial registration: Not applicable.

Background

Late-preterm infants (LPI) (with gestational age between 34+0 and 36+6 weeks) is common in preterm infants. LPI has a higher morbidity of apnea, respiratory distress, kernicterus [1], and mortality rates when compared to term infants [2, 3]. Pediatricians are responsible for caring for these children who might be healthy, but actually, are at higher risks of morbidities.

Vitamin A, a kind of fat-soluble vitamin, has several physiological functions. It plays an essential role in retina growth and differentiation, and the lung. Also, vitamin A maintains epithelial integrity, bone development, and immunity, and promote the maturation of type II alveolar epithelial cells [4-5]. Vitamin A aberration is associated with many diseases, such as night blindness, dry eye, corneal softening, corneal ulcers, immune dysfunction, and respiratory infections. Several studies have reported vitamin A insufficiency to be associated with morbidity of premature infants. With vitamin A deficiency occurring during pregnancy, pulmonary surfactant is poorly produced with reduced phospholipid and protein content [5]. This, in turn, leads to respiratory distress syndrome (RDS). Serum retinol (potent vitamin A) insufficiency increases the risk of severe RDS and adverse pulmonary outcome, such as bronchopulmonary dysplasia (BPD) in preterm

infants <1250g or <29 weeks' gestation [6]. Moreover, Esteban-Pretel et al. suggested that vitamin A deficiency can adversely affect alveolar function, and increase the risk of lung disease [7].

Preterm neonates born with low vitamin A levels have an increased risk of developing chronic lung disease [8]. Besides, preterm infants are susceptible to developing hyperbilirubinemia. This, in part, is due to low vitamin A concentration increasing oxidative damage to red cell membranes instigated by oxidative stress [9]. Also, vitamin A deficiency can reduce both cellular and humoral immunity in intestinal mucosa [10]. Vitamin A deficiency increases gut permeability. However, this harmful effect can be improved with vitamin A supplementation [11]. Similarly, vitamin A supplementation ameliorates butyric acid-induced intestinal mucosal injury in newborn rats [12]. The supplementation of trans-retinoic acid (a kind of vitamin A complex) mitigated intestinal impairment in an animal model of necrotizing enterocolitis (NEC) [13]. Furthermore, vitamin A could regulate intestinal flora, alleviate inflammatory reactions, and enhance intestinal epithelial barrier in NEC [14].

The umbilical cord connects fetus and placenta, and helps in the exchange of waste and nutrients between the fetus and mother. Thus, changes in the composition of cord blood can reflect a specific disease state in newborns. Samples obtained from UCB are easier than from peripheral vessel. Also, umbilical cord puncture does not cause adverse effects in newborns. As such, some studies have investigated UCB biomarkers for predicting neonatal diseases [15, 16].

With insufficient serum vitamin A levels increasing the risk of RDS and adverse pulmonary outcome in very low birth weight infants [6, 17], extremely few studies have investigated the connection between vitamin A levels and LPI morbidity. This study was based on the premise that low UCB vitamin A levels can increase LPI morbidities. We performed analysis on obtained UCB specimens to determine vitamin A levels, and ascertain the relationship between UCB vitamin A levels and LPI morbidities.

Methods

We conducted a prospective cohort study between January 1, 2014, and June 30, 2015 with LPI delivered at Wenlin Maternity and Child Health Care Hospital. The hospital is an upper second-class hospital located in Wenling city, Taizhou city, Zhejiang province. 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. Kendall's sample size calculation principle yields sample sizes 5–10 times the number of variables [18]. In our study, there were 20 variables (10 independent variables, including gender (male, female), gestational age (< 35 weeks, ≥ 35 weeks), 2 of birthweight (< 2500 g, ≥ 2500 g), mode of delivery (vaginal, cesarean section), and UCB vitamin A level (< 0.7μmol/L, ≥ 0.7μmol/L). The 10 of dependent variables included Apgar score (1 min Apgar score ≤ 7, 5 min Apgar score ≤ 7), hospitalization, oxygen supplementation, hyperbilirubinemia, sepsis, RDS, NEC, BPD, and death. Sample size was set at 210; thus, (20x10 = 200). Firstly, we collected UCB specimens to determine vitamin A levels. We then assessed neonatal morbidities during follow-up, investigated the relationship between UCB vitamin A levels and LPI morbidities, and finally, ascertained whether UCB vitamin A levels could predict for LPI morbidities.

Obstetricians or midwives selected 3-ml umbilical blood samples from maternal end of the umbilical cord vein after umbilical cords had been clamped, and cut in the delivery or operating room. Samples were injected into the anticoagulant brown tube, and kept in a dark place. Supernatant was extracted by centrifugal, and preserved at -20^{0}C for subsequent experiments. Vitamin A levels were determined using enzyme-linked immunosorbent assay (ELISA). The accomplished test required 6 vitamin A kits (96 T). Reagent box was used to determine human vitamin A level in the specimen using the double antibody sandwich method. Purified human vitamin antibody package was made into microporous plate to make solid-phase antibodies. Vitamin A was added to microporous pores, and combined with horseradish peroxidase (HRP) labelled vitamin A antibodies to form an antibody-antigen-enzyme labelled antibody complex. After a thorough wash, substrate 3,3',5,5'-tetramethylbenzidine (TMB) colour was added. Using HRP, the color of TMB was transformed to blue, before eventually changing to yellow in the presence of acid. The shades of colour positively correlated with vitamin A in the sample. The absorbance (OD value) was determined at 450 nm wavelength by an enzyme marker, and vitamin A level was calculated by the standard curve.

The following conditions were recorded in study participants during follow-ups: jaundice, sepsis, RDS, BPD, NEC, and death. Pediatricians 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, before being discharged from the hospital. Those without abnormalities adhered to the necessary follow-ups before being discharged.

Definitions

Bilirubin levels were interpreted according to infants' 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 [19, 20]. Oxygen supplementation meant 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 systemic inflammatory response in the presence of or as a result of a suspected or proven infection [21]. RDS was determined based on classic signs of respiratory distress, as well as exclusion of other causes of respiratory failure. RDS diagnosis was confirmed radiologically in cases of reduced lung volume, reticulogranular lung consolidation, and air bronchograms [22]. BPD was identified when there was clinical evidence of BPD, combined with oxygen therapy at 28 days of life [23]. NEC was clinically and radiographically diagnosed using modified Bell's criteria [24]. UCB vitamin A level was divided into two ranges, low vitamin A level < 0.70 μmol/L and vitamin A level ≥ 0.7 μmol/L [6].

Statistical methods

The distribution of data was analyzed by Kolmogorov–Smirnov test. Normal distributed data are expressed as mean ± standard deviation. Continuous variables were compared between 2 groups using student's *t*-test. Non-normally distributed data were expressed as medians (interquartile range), and data compared between 2 groups using Mann-Whitney *U* test. Countable data were expressed as number (%). Data were compared

between groups using chi-square or Fisher's exact test. Univariate and multivariate logistical regression analyses were performed 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 was considered statistically significant. All data were analyzed by IBM Statistical Package for the Social Sciences (SPSS), version 23 (IBM Corporation).

Results

Clinical characteristics of LPI

The study cohort comprised 208 LPI between January 1, 2014, and June 30, 2015. We sampled 210 umbilical cord blood specimens, of which 2 were excluded due to insufficient umbilical cord blood samples. The clinical characteristics and outcomes of the study population are 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 vaginally, while 85 (40.9%) were delivered by cesarean section. Only two (1%) infants had low 1 min Apgar score. Median UCB vitamin A level in LPI was 0.754 (0.656, 0.892) μmol/L. Prevalence of low UCB vitamin A level <0.7 μmol/L was 37.5% (78/208).

Potential factors affecting UCB vitamin A levels

We analyzed various potential factors that may affect UCB vitamin A levels, such as gestational age (< 35 weeks and ≥35 weeks), birth weight (< 2500 g and ≥ 2500 g), 1 min Apgar score ≤ 7, 5 min Apgar score ≤ 7, delivery mode, and gender. In comparison to vaginal delivery, cesarean section was an independent risk factor of UCB vitamin A level < 0.7 μmol/L (*OR* = 6.148，95% *CI* 2.063 – 18.319, *P* = 0.001). Gender, gestational age < 35 weeks , birthweight < 2500g, and gender were not independent risk factors of UCB vitamin A level < 0.7 μmol/L in LPI (table 2).

Relationship between UCB vitamin A levels, other factors and LPI morbidities

We observed relationship between UCB vitamin A levels and LPI morbidities, such as 1 min Apgar score ≤ 7, hospitalization, oxygen supplementation, hyperbilirubinemia, sepsis and RDS. UCB vitamin A level < 0.7μmol/L was not an influence factor of 1 min Apgar score ≤ 7 (*OR* = 0.000, 95% *CI* (0.000-); *P* = 0.997), 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). Despite adjusting confounding factors, such as gender, mode of delivery, gestational age, birthweight, UCB vitamin A level < 0.7 μmol/L was not an influence factor of 1 min Apgar score ≤ 7, hospitalization, oxygen supplementation, hyperbilirubinemia, sepsis, and RDS. Gender had no relationship with these outcomes. However, compared to vaginal delivery, cesarean section was an independent risk factor of hospitalization (*OR* = 2.402, 95% *CI* (1.215-4.758); *P* = 0.012), oxygen supplementation (*OR* =7.863, 95% *CI* (2.999-20.612; *P* = 0.000), and RDS (*OR* = 7.357, 95% *CI* (2.175-24.891); *P* = 0.001). Also, compared to gestational age ≥ 35 weeks, gestational age < 35 weeks was an independent risk factor of hospitalization (*OR* = 2.653, 95% *CI* (1.107-6.360); *P* = 0.029), hyperbilirubinemia (*OR* = 5.305, 95% *CI* (2.175-12.938); *P* = 0.000),and RDS (*OR* =

4.970, 95% *CI* (1.646-15.004); *P* = 0.004). In addition, compared to birthweight ≥ 2500 g, birthweight < 2500 g was an independent risk factor of hospitalization (*OR* =2.721, 95% *CI* (1.346-5.501); *P* = 0.005) and RDS (*OR* =3.342, 95% *CI* (1.094-10.204); *P* = 0.034) (tables 3–5).

Discussion

In this study, we analyzed UCB vitamin A levels, and its relationship with some medical morbidities in LPI. The median UCB vitamin A level of LPI was 0.754 (0.656, 0.892) μmol/L (table 1). Our median UCB vitamin A level was higher than a previous study where UCB vitamin A level of 0.55 ± 0.17 μmol/L was reported [24]. However, that study did not mention the birth weight of LPI. In another study, UCB vitamin A level less than 1.05 μmol/L were measured in 22/56, and levels below 0.7 μmol/L only measured in 2/56 for gestational age < 33 weeks [8]. These results were inconsistent. Two probable reasons were the different gestational age and birthweight of study participants. Nevertheless, preterm infants are prone to low vitamin A level [25]. Our results showed the prevalence of low UCB vitamin A levels <0.7 μmol/L in LPI to be high (37.5%, 78/208). Several reasons could have accounted for this. For example, fetuses cannot synthesize vitamin A, and thus, primarily depend on maternal placental supply in late pregnancy [26]. Also, retinol-binding protein (RBP) manufactured in the fetal liver during the final quarter of pregnancy plays a vital role in fetal vitamin A transportation. Premature infants are unable to synthesize enough RBP to transport vitamin A [27, 28]. This results in preterms being susceptible to having low vitamin A level.

We compared the effect of various factors on vitamin A levels, including gestational age, birth weight, 1 min Apgar score, 5 min Apgar score, delivery mode, and gender. LPI delivered via cesarean section is more likely to be low UCB vitamin A level < 0.7 μmol/L than those delivered via the vagina (table 2). Cesarean section was an independent factor for low UCB vitamin A level < 0.7 μmol/L. Vaginal deliveries without anesthesia are more stressful than cesarean deliveries, and this stress can increase maternal corticosteroids [29]. Corticosteroids increase placental cord concentrations of vitamin A [30]; hence the lower and higher UCB vitamin A levels in cesarean section and vaginal deliveries, respectively. Contrastingly, Gonzalez- Corbella et al. reported no significant difference in vitamin A levels between vaginal and cesarean deliveries [30]. We believe their inconsistent results had to do with the lower study participants (35 vaginal and 21 cesarean deliveries). Thus, based on our results, we are of the view that UCB vitamin A levels are significantly lower in cesarean section than vaginal delivery. Additionally, vitamin A levels in our study were not associated with birth weight, gestational age, and gender in LPI. These results were in line with previous studies [8, 30]. Retinol is significantly higher in the sera of mothers giving preterm births as a result of preterm premature rupture of membranes [31]. Thus, preterm premature rupture of membranes could affect vitamin A levels; nonetheless, the exact mechanisms is yet to be comprehensively elucidated.

Vitamin A acts on lung's retinoic acid receptors to upregulate the transcription and expression of surfactant protein-B gene. This, in turn, promotes the synthesis of pulmonary surfactant [32]. Besides, mild vitamin A deficiency has been shown to delay fetal lung maturation in animal studies. Surfactant proteins – A, B, and C messenger RNAs were decreased by 46%, 32%, and 28%, respectively, in vitamin A deficient fetuses [5]. Kiatchoosakun et al. suggested that vitamin A supplementation can reduce intubation time and oxygen supplementation, while also shortening the length of hospital stay [33]. However, another study reported no

difference in the duration of oxygen therapy between vitamin A supplementation and control groups [34]. In our study, we found vitamin A level < 0.7 μmol/L to not be an independent risk factor for hospitalization, oxygen supplementation, and RDS in LPI (table 3-5). Our result was consistent with a previously reported study [8]. Therefore, vitamin A can promote lung surfactant synthesis, and thus, enhance lung maturation. However, this might not have a significant effect on LPI who have relatively matured lungs than other preterm infants. Having said that, further studies are warranted to clarify this.

Vitamin A can regulate specific and non-specific immunity, and protect against bacterial infection as an antioxidant [35]. Plasma vitamin A concentrations are decreased during airway infection in premature neonates [36]. In our study, however, UCB vitamin A level < 0.7 μmol/L was not an independent risk factor for sepsis (table 3).

We also found UCB vitamin A level < 0.7 was not an independent risk factor for hyperbilirubinemia in LPI (table 4). To the best our knowledge, there are limited studies reporting an association between vitamin A concentration and hyperbilirubinemia in LPI. As such, larger sample studies based on specific population are needed to corroborate this relationship. In addition, none of the neonates in this study suffered from BPD, NEC, and death. Thus, the relationship between UCB vitamin A levels and BPD, NEC or death in LPI requires further study.

Cesarean section, in this study, was an independent risk factor of not only hospitalization and oxygen supplementation, but also RDS (table 3-5). This result is supported by a recent meta-analysis. The authors reported that cesarean section was associated with an increased risk of neonatal RDS [37], with the underlying reason being the release of catecholamine [38]. A high concentration of catecholamine in newborn infants promotes lung fluid absorption, and increases the release of surfactants [39]. Hence, cesarean section increases the risk for RDS in LPI, which in turn, increases the risk of hospitalization and oxygen supplementation. Additionally, in comparison to gestational age ≥ 35 weeks, gestational age < 35 weeks increased the risk of hospitalization, hyperbilirubinemia and RDS. Thus, LPI of gestational age < 35 weeks are at more risk than those at gestational age ≥ 35 weeks. Similarly, compared to birthweight ≥ 2500 g, birth weight < 2500 g increases the risk of hospitalization and RDS. As such, these late preterm infants would need more attention.

It is worth noting that our present study has limitations. For example, the number of study participants was small. Besides, the study does not include the umbilical cord samples of term infants as control group of the study, although we did a subgroup analysis. Also, we did not measure other vitamins or micronutrients, which possibly might have an impact on the results.

Conclusions

Low umbilical cord blood vitamin A levels are common among late-preterm infants. Cesarean section delivery is an independent risk factor for low umbilical cord blood vitamin A level and increases the risk for RDS. However, on the basis of our results, there is no correlation between low vitamin A level and LPI morbidities, including hyperbilirubinemia, sepsis, and RDS.

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. 2013-01218). Written informed consent was obtained from the mother or legal guardian of each neonate before inclusion into the 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 analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Conceptualization and methodology: T-MY. Collection and recording of specimens C-EC, L-YC. Follow-up and management of late-preterm infants: C-EC, Y-QC, E-FT. Analysis, writing, original draft preparation: E-FT. Writing - review and editing: T-M Y. All authors read and approved the final manuscript.

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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.

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Tables

Table 1. Clinical characteristics of late-preterm infants

Variable / category	N (%) / Mean (Standard deviation)
Sex	
male	112 (53.8)
female	96 (46.2)
Gestational age (Weeks)	35.68 ± 0.74
Birthweight（g）	2613.32 ± 425.57
Mode of delivery	
Vaginal	123 (59.1)
Cesarean section	85 (40.9)
1 min Apgar score ≤ 7	2（1）
5 min Apgar score ≤ 7	0（0）
UCB vitamin A level	
<0.7 μmol/L	78 (37.5)
≥ 0.7 μmol/L	130 (62.5)
Hospitalization	51 (24.5)
Oxygen supplementation	32 (15.4)
Hyperbilirubinemia	50 (24)
Sepsis	9 (4.3)

Table 1. Clinical characteristics of late preterm infants

Variable / category	N (%) / Mean (Standard deviation)
RDS	21 (10.1)
BPD	0 (0)
NEC	0 (0)
Death	0 (0)

N = 208

Abbreviations: UCB: umbilical cord blood, RDS: respiratory distress syndrome, BPD: bronchopulmonary dysplasia, NEC: necrotizing enterocolitis, N: number of study participants

Table 2. Potential factors associated with UCB vitamin A level < 0.7 µmol/L

Factors	*OR* (95% *CI*)	*P*
Male	0.724 (0.329-1.594)	0.422
(Reference category: Female)		
Cesarean section	6.148 (2.063-18.319)	0.001
(Reference category: Vaginal)		
Gestational age (< 35 weeks)	0.809 (0.210-3.119)	0.758
(Reference category: ≥35 weeks)		
Birthweight (< 2500 g)	0.455 (0.178-1.160)	0.099
(Reference category: ≥ 2500 g)		

Data were analyzed by multivariate logistic regression analysis

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

Table 3 Effect of UCB vitamin A level < 0.7 µmol/L on 1 min Apgar score ≤ 7 and hospitalization

Factors		Univariate		Multivariate		Univariate		Multivariate	
		OR (95% *CI*)	*P*	*OR* (95% *CI*)	*P*	*OR* (95% *CI*)	*P*	*OR* (95% *CI*)	*P*
UCB vitamin A level	< 0.7 µmol/L	0.000 (0.000--)	0.997	0.000 (0.000--)	0.996	1.368 0.719-2.603	0.339	0.944 (0.467-1.911)	0.873
	≥ 0.7 µmol/L	1							
Gender	Male	0.856 (0.053-13.869)	0.913	0.680 (0.025-18.346)	0.973	0.859 0.456-1.616)	0.637	0.988 (0.499-1.959)	0.973
	Female	1							
Mode of delivery	Cesarean section	0.000 (0.000--)	0.996	0.000 (0.000--)	0.996	2.649 (1.387-5.059)	**0.003**	2.404 (1.215-4.758)	**0.012**
	Vaginal	1							
Gestational age	< 35 weeks	0.164 (0.010-2.693)	0.205	6.567 (0.238-180.994)	0.266	3.944 (1.766-8.811)	**0.001**	2.653 (1.107-6.360)	**0.029**
	≥35 weeks	1							
Birthweight	< 2500 g	0.000 0.000--	0.996	--	0.995	3.447 (1.791-6.637)	**0.000**	2.721 (1.346-5.501)	**0.005**
	≥ 2500 g	1							
		Outcome: 1 min Apgar score ≤ 7				Outcome: Hospitalization			

Data were analyzed by univariate and multivariate logistic regression analysis (N = 208)

Abbreviations: UCB: umbilical cord blood, RDS: respiratory distress syndrome, OR: odds ratio, CI: confidence interval, N: Number of study participants

Figures

Table 4 Effect of UCB vitamin A level < 0.7 µmol/L on oxygen supplementation and hyperbilirubinemia

Factors		Univariate		Multivariate		Univariate		Multivariate	
		OR (95% *CI*)	*P*	*OR* (95% *CI*)	*P*	*OR* (95% *CI*)	*P*	*OR* (95% *CI*)	*P*
UCB vitamin A level	< 0.7 µmol/L	1.839 (0.861-3.927)	0.116	1.263 (0.544-2.934)	0.587	0.819 (0.420-1.596)	0.558	0.520 (0.244-1.107)	0.090
	≥ 0.7 µmol/L	1							
Gender	Male	0.719 (0.338-1.529)	0.391	0.894 (0.385-2.075)	0.794	1.008 0.533-1.908)	0.980	1.115 (0.559-2.224)	0.757
	Female	1							
Mode of delivery	Cesarean section	8.593 (3.353-22.026)	**0.000**	7.863 (2.999-20.612)	**0.000**	0.550 (0.290-1.045)	0.068	1.693 (0.848-3.381)	0.136
	Vaginal	1							
Gestational age	< 35 weeks	3.545 (1.47-8.553)	0.005	2.304 (0.827-6.418)	0.110	5.746 (2.543-12.982)	**0.000**	5.305 (2.175-12.938)	**0.000**
	≥35 weeks	1							
Birthweight	< 2500 g	3.051 (1.409-6.609)	0.005	2.258 (0.940-5.421)	0.068	2.340 (1.224-4.474)	0.010	1.755 0.851-3.617)	0.128
	≥ 2500 g	1							
		Outcome: Oxygen supplementation				Outcome: Hyperbilirubinemia			

Data were analyzed by univariate and multivariate logistic regression analysis (N = 208)

Abbreviations: UCB: umbilical cord blood, RDS: respiratory distress syndrome, OR odds ratio, CI: confidence interval, N: number of study participants

Table 5 Effect of UCB vitamin A level < 0.7 µmol/L on Sepsis and RDS

Factors		Univariate		Multivariate		Univariate		Multivariate	
		OR (95% *CI*)	*P*	*OR* (95% *CI*)	*P*	*OR* (95% *CI*)	*P*	*OR* (95% *CI*)	*P*
UCB vitamin A level	< 0.7 µmol/L	2.158 (0.562-8.289)	0.263	1.775 (0.441-7.145)	0.419	2.444 0.979-6.102	0.055	1.603 (0.573-4.485)	0.369
	≥ 0.7 µmol/L	1							
Gender	Male	0.413 (0.100-1.697)	0.220	0.454 (0.108-1.914)	0.282	0.937 0.380-2.312)	0.887	1.511 (0.517-4.414)	0.451
	Female	1							
Mode of delivery	Cesarean section	0.329 (0.080-1.355	0.124	2.514 (0.589-10.729)	0.213	7.437 (2.404-23.006)	**0.000**	7.357 (2.175-24.891)	**0.001**
	Vaginal	1							
Gestational age	< 35 weeks	1.745 (0.345-8.830)	0.501	1.015 (0.170-6.073)	0.987	7.591 (2.866-20.102)	**0.000**	4.970 (1.646-15.004)	**0.004**
	≥35 weeks	1							
Birthweight	< 2500 g	2.254 0.586-8.661	0.237	1.774 (0.412-7.638)	0.442	5.164 (1.909-13.965)	**0.001**	3.342 (1.094-10.204)	**0.034**
	≥ 2500 g	1							
		Outcome: Sepsis				Outcome: RDS			

Data were analyzed by univariate and multivariate logistic regression analysis (N = 208)

Abbreviations: UCB: umbilical cord blood, RDS: respiratory distress syndrome, OR: odds ratio, CI: confidence interval, N: number of study participants

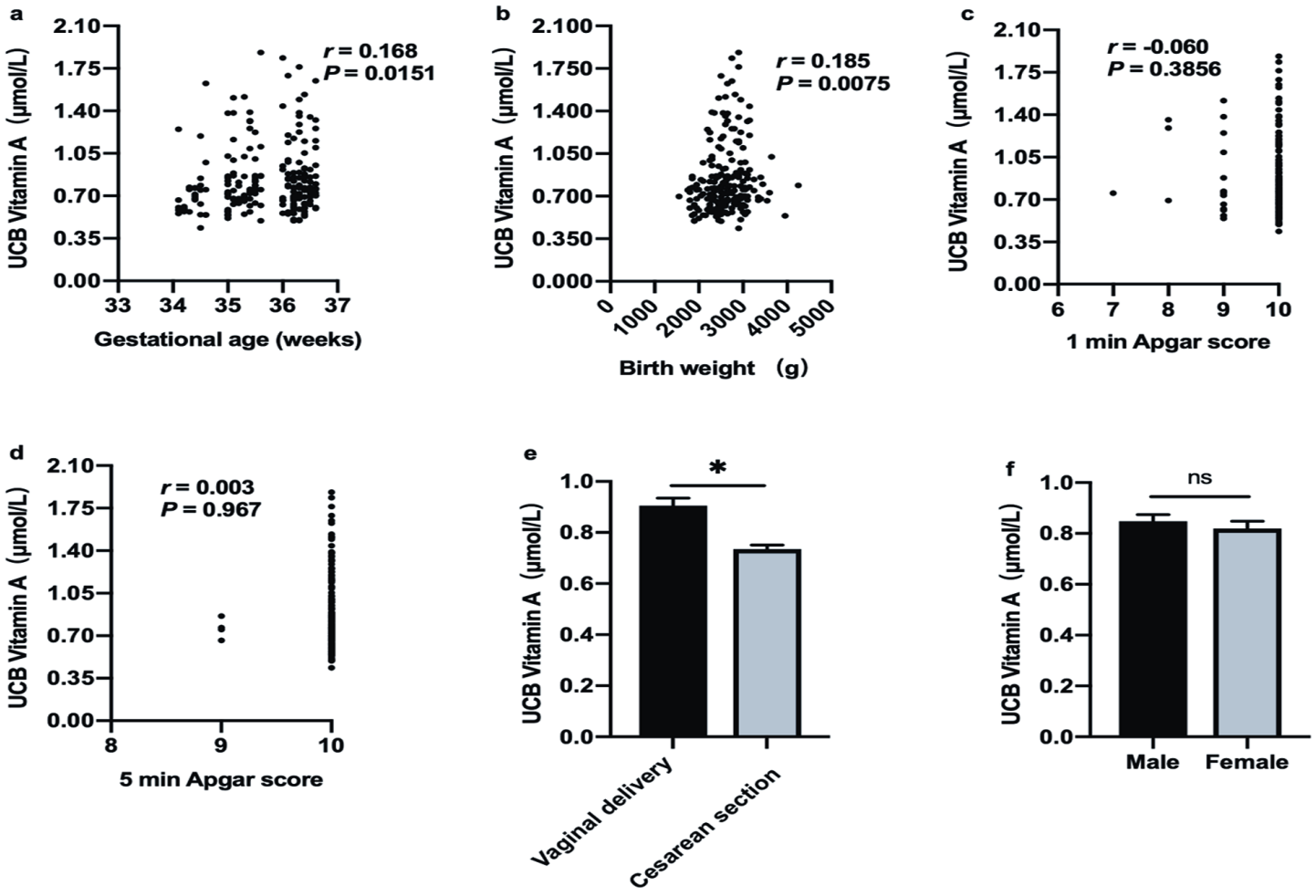

Figure 1

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

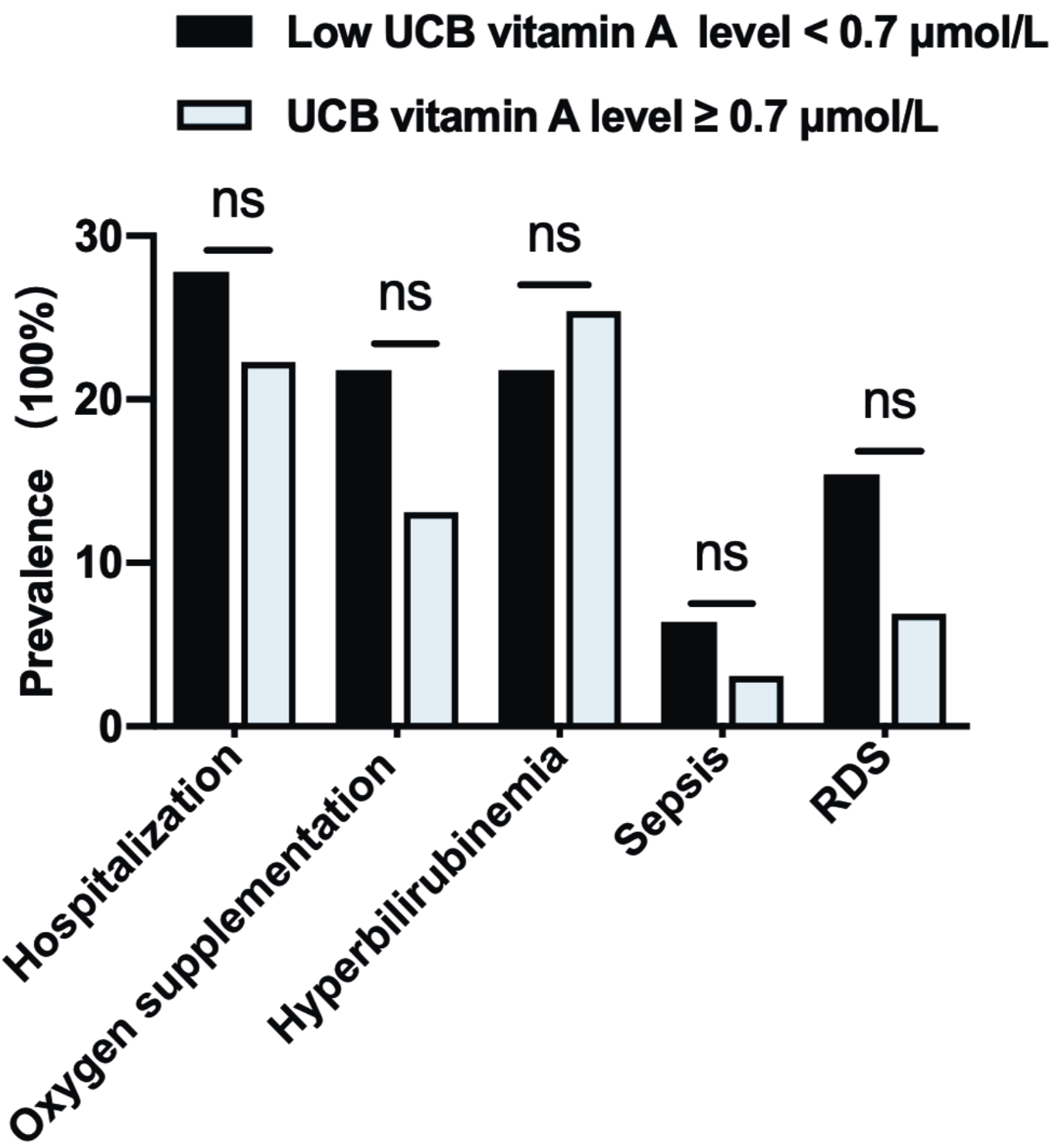

Figure 2

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 $P > 0.05$).