The Turkish Journal of Pediatrics 2022; 64: 605-611
https://doi.org/10.24953/turkjped.2021.5011

Original Article

Association between serum vitamin A, D and E status and respiratory distress syndrome in preterm infants – a propensity score matching analysis

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ABSTRACT

Background. This study aimed to assess whether the serum levels of vitamin A, vitamin D and vitamin E are associated with respiratory distress syndrome (RDS) in preterm infants.

Methods. This retrospective research included 179 neonates born before 35 weeks of gestation in Jiaxing Maternity and Child Health Care Hospital from January 2020 to December 2020. Depending on whether or not they had RDS, participants were classified into the RDS group (59 neonates) and the control group (120 neonates). The 1:1 propensity score matching (PSM) analysis was performed to balance the baseline confounding factors and then the groups were compared in terms of serum vitamin levels and RDS morbidity.

Results. A total of 34 pairs of preterm infants were involved after PSM. There were significant differences in vitamin D level (12.13 (8.44-17.85) ng/mL vs. 16.84 (10.75-25.83) ng/mL), vitamin D deficiency rate (85.3% vs. 55.9%), as well as vitamin A level (134.91 (105.01-156.74) ng/mL vs. 152.46 (120.06-200.00) ng/mL) in the two groups. However, the vitamin A deficiency rate, vitamin E status, as well as vitamin E deficiency rate did not differ significantly between the two groups. Logistic analysis showed that a low level of vitamin D was an independent risk factor for RDS in preterm neonates (*OR 0.917, 95%CI 0.851-0.989*).

Conclusions. Low serum vitamin D levels may contribute to the development of RDS in preterm infants, but no significant effect of serum vitamin A and vitamin E levels was found.

Key words: vitamin A, vitamin D, vitamin E, respiratory distress syndrome, propensity score matching.

Respiratory distress syndrome (RDS) is known as a major complication in preterm infants and also one of the important causes of neonatal death, with structural immaturity of lung development and deficiency of pulmonary surfactant (PS) being key factors in its pathogenesis.[1] Vitamin A (Vit A), vitamin D (Vit D) and vitamin E (Vit E) are all fat-soluble vitamins whose metabolites are important ligands for several transcription factors and are involved in various biological processes in the body.[2,3] It has been shown that Vit A, Vit D and Vit E can play essential roles in the growth and development, metabolism, and immune regulation of the body.[4] Some previous studies have shown a positive effect of Vit D on neonatal respiratory diseases[5-7], but there are few systematic studies that focus on the relationship between fat-soluble vitamins and RDS in preterm neonates. In this study, we investigated the relationship between serum Vit A, Vit D and Vit E status and RDS in preterm infants by using the propensity score matching (PSM) method to balance the confounding factors between subgroups, with the aim of providing a basis for early prevention and treatment of RDS in preterm neonates.

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Received 9th November 2021, revised 19th December 2021, accepted 15th February 2022.

Material and Methods

Group setting and data collection

According to the inclusion and exclusion criteria, preterm infants hospitalized in the neonatal intensive care unit of Jiaxing Maternity and Child Health Care Hospital from January 2020 to December 2020 were selected, in which those diagnosed with RDS were admitted to the RDS group while others without RDS were admitted to the control group.

This research was approved by the Medical Ethics Committee of Jiaxing Maternity and Child Health Care Hospital (No. 2020-3).

Inclusion criteria: ① gestational age at birth ≤ 35 weeks; ② admission within 24 hours after birth and complete serum Vit A, 25-hydroxyvitamin D (25(OH)Vit D) and Vit E determination; ③ informed consent from guardians; ④ complete clinical case data.

Exclusion criteria: ① congenital genetic metabolic diseases or malformations; ② combined with liver and kidney diseases or thyroid function abnormalities; ③ maternal presence of liver and kidney function abnormalities, thyroid function abnormalities, bone metabolic diseases or anticonvulsant, epilepsy, tuberculosis drugs during pregnancy.

Maternal and neonatal characteristics were collected from the medical record database, including single or twin gestation, sex, birth weight, gestational age (GA), season of birth, mode of delivery, Apgar scores at 1 and 5 min, maternal age, maternal body and mass index (BMI), antenatal steroid use, presence of premature rupture of membranes (PROM), gestational hypertension, as well as gestational diabetes mellitus (GDM). Serum concentrations of Vit A, 25(OH)Vit D and Vit E of preterm infants were determined from peripheral blood samples taken within 24 hours of life and measured by mass spectrometry.

Diagnostic criteria

Neonatal RDS was diagnosed using the 2017 edition of the Montreux definition.[8] Vit A <200 ng/mL was defined as Vit A deficiency, 25(OH) Vit D <20 ng/mL as Vit D deficiency, and Vit E <5 μg/mL as Vit E deficiency in accordance with the relevant association standards.[9,10]

Statistical analysis

All the data were analyzed by SPSS software (SPSS Inc., Chicago, IL) version 22.0.

Logistic regression was used for propensity score calculation from baseline patient characteristics. Matching based on propensity scores incorporating different sets of covariates was performed using a 1:1 nearest-neighbor algorithm, with a caliper width of 0.1. For continuous variables, data that matched normal distribution were expressed as mean ± standard deviation and compared by using the Student's t-test, while non-normally-distributed data were presented as medians (interquartile range) and compared using Wilcoxon test. Categorical data were expressed as number (percentage) and the chi-square test was used for comparison. It should be noted that paired t-test and McNemar's test were applied for comparison of continuous and categorical variables respectively after PSM. Variables with a p-value < 0.05 in the univariate analysis were selected for the multivariable analysis. Binary logistic regression analysis was used to investigate whether vitamin levels were independently associated with the occurrence of RDS. A p-value of <0.05 was considered statistically significant.

Results

Comparison of maternal and neonatal characteristics between the two groups before and after PSM

A total of 179 preterm infants who met the selection criteria were enrolled in this study.

Of them, 59 were admitted to the RDS group, whereas 120 were admitted to the control group. After PSM in a 1:1 ratio, 34 pairs of neonates were successfully matched and included for analysis. The baseline characteristics of the patients before and after PSM were summarized in Table I.

Before PSM, the between-group differences in single fetus (*P=0.001*), sex (*P=0.006*), birth weight (*P=0.000*), gestational age (*P=0.000*), Apgar score at 1 min (*P=0.000*) and 5 min (*P=0.000*), as well as the incidence of PROM (*P=0.048*) and gestational hypertension (*P=0.029*) were significant. After PSM, all p-values between groups were greater than 0.1 for the comparison of the listed maternal and neonatal characteristics.

Comparison of serum Vit A, 25(OH)Vit D, and Vit E concentrations in the two groups after PSM

The serum concentrations of Vit A and Vit D in the RDS group were 134.91 (105.01-156.74) ng/mL and 12.13 (8.44-17.85) ng/mL respectively, which were significantly lower than those in the control group. Moreover, the Vit D deficiency rate in the RDS group was observed as 85.3%, which was higher than that in the control group, with statistically significant differences (*P<0.05*). However, no between-group significant differences were observed in the comparison of Vit A deficiency rate, serum Vit E level, and Vit E deficiency rate (*P>0.05*). For details, see Table II.

Table I. Comparison of baseline characteristics between the two groups before and after PSM.

baseline characteristics	before PSM				after PSM			
	RDS group (n=59)	control group (n=120)	$t/Z/\chi 2$	*P*	RDS group (n=34)	control group (n=34)	*t/Z*	*P*
single fetus, n (%)	43 (72.9%)	56 (46.7%)	10.996	0.001	24 (70.6%)	29 (85.3%)	-	0.227
male, n (%)	38 (64.4%)	51 (42.5%)	7.593	0.006	17 (50.0%)	17 (50.0%)	-	1.000
birth weight (g), $\bar{x}\pm s$	1556±398	1801±375	-4.035	0.000	1675±363	1686±388	-0.126	0.900
GA at birth (week), $\bar{x}\pm s$	30.71±1.81	32.57±1.53	-7.197	0.000	31.53±1.56	31.76±1.84	-0.619	0.540
season of birth, n (%)								
spring (March – May)	19 (32.2%)	36 (30.0%)			10 (29.4%)	8 (23.5%)		
summer (June – August)	15 (25.4%)	35 (29.2%)			8 (23.5%)	9 (26.5%)		
autumn (September – Novenber)	7 (11.9%)	21 (17.5%)	1.856	0.603	2 (5.9%)	6 (17.6%)	4.510	0.608
winter (December – February)	18 (30.5%)	28 (23.3%)			14 (41.2%)	11 (32.4%)		
cesarean, n (%)	47 (79.7%)	85 (70.8%)	1.592	0.207	28 (82.4%)	23 (67.6%)	-	0.267
Apgar score at 1 min, *M (IQR)*	7 (6-8)	8 (8-8)	-5.787	0.000	8 (7-8)	7 (7-8)	-1.054	0.292
Apgar score at 5 min, *M (IQR)*	8 (7-8)	8 (8-8)	-5.562	0.000	8 (7-8)	8 (7.75-8)	-0.832	0.405
maternal age (year), $\bar{x}\pm s$	30.80±5.13	29.71±4.87	1.382	0.169	31.24±5.39	30.59±4.34	0.551	0.585
matemal BMI, $\bar{x}\pm s$	25.37±2.44	26.37±3.51	-1.971	0.050	25.63±2.33	25.39±3.77	0.317	0.753
antenatal steroid use, n (%)	49 (83.1%)	102 (85.0%)	0.114	0.736	29 (85.3%)	28 (82.4%)	-	1.000
PROM, n (%)	17 (28.8%)	53 (44.2%)	3.915	0.048	13 (38.2%)	13 (38.2%)	-	1.000
gestational hypertension, n (%)	13 (22.0%)	12 (10.0%)	4.767	0.029	4 (11.8%)	6 (17.6%)	-	0.687
GDM, n (%)	11 (18.6%)	22 (18.3%)	0.003	0.960	9 (26.5%)	6 (17.6%)	-	0.607

- McNemar's test, no statistics

PSM: propensity score matching, IQR: interquartile range, GA: gestational age, BMI: body and mass index, PROM: premature rupture of membranes, GDM: gestational diabetes mellitus

Table II. Comparison of vitamin levels and deficiency rate between the two groups after PSM.

vitamin levels and deficiency rate	RDS group (n=34)	control group (n=34)	*Z*	*P*
Vit A (ng/mL), *M (IQR)*	134.91(105.01-156.74)	152.46 (120.06-200.00)	-2.317	0.021*
Vit A deficiency rate, n (%)	32 (94.1%)	26 (76.5%)	-	0.109
25(OH)Vit D (ng/mL), *M (IQR)*	12.13 (8.44-17.85)	16.84 (10.75-25.83)	-2.445	0.014*
Vit D deficiency rate, n (%)	29 (85.3%)	19 (55.9%)	-	0.006**
Vit E (μg/mL), *M (IQR)*	2.74 (2.24-3.54)	3.00 (2.67-3.60)	-1.086	0.278
Vit E deficiency rate, n (%)	32 (94.1%)	30 (88.2%)	-	0.687

**P<0.05, **P<0.01*, - McNemar's test, no statistics
PSM: propensity score matching, IQR: interquartile range, Vit A: vitamin A, 25(OH)Vit D: 25-hydroxyvitamin D, Vit D: vitamin D, Vit E: vitamin E

Logistic regression analysis of the effect of vitamin levels on RDS in preterm infants

When the univariate analysis was conducted, the serum levels of Vit A and Vit D were considered as possible risk factors for neonatal RDS. Thus, we took Vit A and Vit D levels as covariates and the occurrence of RDS as the dependent variable. Multivariate analysis showed that low serum Vit D level was an independent risk factor for the development of RDS in preterm infants (*OR 0.917, 95% CI 0.851-0.989*), as detailed in Table III.

Discussion

RDS is a common complication of prematurity and presents as progressive dyspnea, cyanosis and respiratory failure within hours of birth. Related studies have shown that combined RDS can increase neonatal mortality by more than three times.[11] Therefore, our study investigates the relationship between different fat-soluble vitamins and RDS, providing new strategies for the prevention and treatment of RDS in preterm infants from a vitamin perspective.

In our study, the comparison between the groups was adjusted for confounding variables with PSM to minimize selection bias, and thus the baseline characteristics of the RDS and control groups were equalized and comparable.

Vit A is involved in the growth and differentiation of airway epithelial cells, maintaining their structural and functional integrity to act as a barrier.[12] Also, Vit A acts on the lung's retinoic acid receptors to upregulate the transcription and expression of the surfactant protein-B gene and thus promotes the synthesis of pulmonary surfactant.[13] In addition, Vit A has demonstrated an effect on the proliferation and differentiation of T cells to perform immunoregulatory functions.[14] Studies in animal models have confirmed that Vit A plays a key role in lung injury prevention.[15] Chen et al.[16] also reported that Vit A deficiency is associated with an increased risk of adverse lung outcomes in newborns. The results of our study showed that after PSM, although serum Vit A levels were significantly lower in preterm infants in the RDS group than that in the control group (*P<0.05*), logistic regression analysis did not suggest a significant effect of low serum Vit A levels on the development of RDS in preterm infants. It might be related to the fact that serum Vit A levels do not fully reflect the local Vit A concentration within the lung epithelial tissue. Therefore, the correlation between serum Vit A levels and the development of RDS in preterm infants still requires further study.

Table III. Logistic regression analysis

Covariates	*B*	*S.E.*	*Wald*	*P*	*OR*	*95%CI*
Vit A	-0.008	0.006	2.076	0.150	0.992	0.980-1.003
Vit D	-0.086	0.038	5.074	0.024	0.917	0.851-0.989

Vit A: vitamin A, Vit D: vitamin D

Vit D is a steroid hormone, and recent studies have identified its more extraosseous influence, especially positive effects on the regulation of lung maturation and development, such as the impact on alveolar type II cells, fibroblast proliferation, surfactant synthesis, alveolarization, and upregulation of vitamin D receptor in the lungs.[17] The research conducted by Dogan[18] and Treiber et al.[19] also confirmed that preterm infants with RDS are born with lower Vit D levels. The results of our study showed that after PSM, serum Vit D levels were lower in the RDS group of preterm infants than that in the control group, with a significant difference. ($P<0.05$). Furthermore, logistic regression analysis suggested that Vit D deficiency was an independent risk factor for the development of RDS in preterm infants. Therefore, Vit D supplementation may have a positive effect on preventing the occurrence and development of RDS in preterm infants.

Vit E, also known as tocopherol, is a potent antioxidant capable of neutralizing free radicals and reactive oxygen species by providing hydrogen ions through its chromogranin ring.[20,21] Oxidative stress-mediated cellular damage is thought to underlie the pathophysiology of respiratory distress syndrome, and antioxidant vitamins are thought to inhibit the harmful effects of free radicals and have protective potential in the therapy of acute respiratory distress syndrome.[22] However, our present study did not find significant differences either in Vit E levels or deficiency rates between the RDS and control preterm infants after PSM, which may be explained by the fact that low antioxidant plasma levels may not necessarily indicate low total body stores as the critical illness itself may induce redistribution of antioxidants.[23] Although animal experiments have shown that nebulized inhaled Vit E improves ventilation parameters and has a potential benefit on lung disease, it has not been confirmed in human studies.[24] Therefore, the correlation between serum Vit E levels and the development of RDS in preterm infants is not definitive and further studies are warranted to clarify this.

In conclusion, the present study concluded that Vit A, Vit D and Vit E deficiencies are more common in preterm infants and that low serum Vit D levels are an independent risk factor for the development of RDS, but no significant effect of serum Vit A and Vit E on RDS in preterm infants was found, which needs to be further confirmed by studies with larger sample sizes. Adequate Vit D supplementation during pregnancy is expected to reduce the incidence of RDS in preterm infants, but the amount of supplementation needs to be further studied.

Acknowledgement

The author would like to thank Xiaoyi Ji MD from the Department of Pediatrics for her guidance in this study.

Ethical approval

This study was approved by the Medical Ethics Committee of Jiaxing Maternity and Child Health Care Hospital (No. 2020-3).

Author contribution

The author confirms contribution to the paper as follows: study conception and design: YYZ; data collection: YYZ; analysis and interpretation of results: YYZ; draft manuscript preparation YYZ. All authors reviewed the results and approved the final version of the manuscript.

Source of funding

This study was supported by Zhejiang Provincial Medical and Health Science and Technology Project (2021KY1122).

Conflict of interest

The authors declare that there is no conflict of interest.

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