

Research Article

## Low Vitamin D Levels Increase the Risk of Early Onset Neonatal Sepsis

### Kadar vitamin D yang Rendah Meningkatkan Risiko Sepsis Neonatal Awitan Dini

<sup>1</sup>Lisnawati Yuyun, <sup>2</sup>Ali Sungkar, <sup>3</sup>Rinawati Rohsiswatno, <sup>2</sup>Noroyono Wibowo,  
<sup>2</sup>Denni Hermartin, <sup>2</sup>Agustin Kindi

<sup>1</sup>Department of Obstetrics and Gynecology  
Persahabatan Hospital, Jakarta

<sup>2</sup>Department of Obstetrics and Gynecology

<sup>3</sup>Department of Pediatrics

Faculty of Medicine Universitas Indonesia

Dr. Cipto Mangunkusumo General Hospital, Jakarta

#### Abstract

**Objective:** To identify the association between maternal and umbilical cord vitamin D levels with suspects of Early-Onset of Neonatal Sepsis (EONS) in newborns from mothers with Preterm Premature Rupture of Membranes (PPROM).

**Methods:** This is a retrospective cohort study conducted from January 2017 to August 2018. Data was taken consecutively from medical records and previous study data at Dr. Cipto Mangunkusumo and Persahabatan Hospital, Jakarta.

**Results:** From total of 72 infants from mothers with PPRM, 22 infants (31%) were EONS-suspected and 50 infants (69%) were not EONS-suspected. There was a significant association between maternal and umbilical cord vitamin D levels with EONS.

**Conclusions:** There was a significant association between maternal and umbilical cord vitamin D levels with EONS.

**Keywords:** early-onset neonatal sepsis, preterm premature rupture of membrane, vitamin D.

#### Abstrak

**Tujuan:** Untuk mengetahui hubungan antara kadar vitamin D maternal dan tali pusat dengan risiko terjadinya Sepsis Neonatal Awitan Dini (SNAD) pada bayi dari ibu dengan Ketuban Pecah Dini (KPD).

**Metode:** Desain penelitian kohort retrospektif secara consecutive sampling. Data diambil dari rekam medis dan data penelitian sebelumnya di Rumah Sakit Umum Pusat Nasional (RSUPN) Dr. Cipto Mangunkusumo dan Rumah Sakit Umum Pusat (RSUP) Persahabatan, Jakarta.

**Hasil:** Dari 72 bayi yang dilahirkan dari ibu dengan KPD, 22 bayi (31%) diantaranya diduga mengalami SNAD, sedangkan 50 bayi lainnya tidak mengalami SNAD. Terdapat hubungan yang bermakna antara kadar vitamin D maternal dan tali pusat dengan kejadian SNAD.

**Kesimpulan:** Terdapat hubungan yang bermakna antara kadar vitamin D maternal dan tali pusat dengan kejadian SNAD.

**Kata kunci:** ketuban pecah dini, sepsis neonatal awitan dini, vitamin D.

**Correspondence author.** Denni Hermartin. deny.hermartin@gmail.com

#### INTRODUCTION

The common cause (70%) of perinatal death was preterm birth. Preterm neonates often failed to adapt to new environment, causing high morbidity and mortality.<sup>1,2</sup> It was important to decrease neonatal (0-28 days of age) mortality rate because it was contributed to 59% of infant mortality. Indonesian Demographic and Health Survey 2012 showed the neonatal mortality rate during 2012 was 19 per 1.000 live births.<sup>3</sup> Based on RISKESDAS 2007, neonatal sepsis (12%) was one of the common cause of neonatal death during 0-6 days of life besides respiratory

disorders (37%), prematurity (34%), hypothermia (7%), icterus neonatorum (6%), and congenital abnormality (1%).<sup>4</sup>

Vitamin D played an important role to modulate the immune system. Vitamin D deficiency was associated with decrease in production of antimicrobial substances. A few studies showed that vitamin D concentration circulated in the umbilical cord was indirectly correlated with newborns susceptibility getting infection.<sup>5</sup>

The incidence rate of preterm premature rupture of membranes was 3-10% from all of

labour, 4% was happened in gestational age less than 34 weeks. Incidence rate of PPRM in Indonesia was approximately 35.7-55.3% from 17.665 labour. PPRM was one of preterm birth cause related to high perinatal morbidity and mortality. Preterm birth was happened in 1 of 10 labor in United State and the number was higher in developing countries, about 40-75% neonatal death.<sup>6,7</sup>

A cross-sectional study in Tertiary Obstetrics and Gynecology Center in Kosovo which total of 200 newborns from pregnant women with PPRM was involved. In this study, there were 13% newborns with early-onset neonatal infection, while 5% of them were neonatal sepsis cases.

## METHODS

This study was a retrospective cohort study conducted at Dr. Cipto Mangunkusumo and Persahabatan Hospital from January 2017 to Augusts 2018. The population in this study was pregnant women with preterm premature of the membrane (PPROM) and their newborn in 28-34 weeks' gestation. The inclusion criteria of subjects were pregnant women with PPRM and born in 28-34 weeks gestation, complete data, mother and her baby data matched, the neonates were hospitalised in NICU minimal 3 days and the exclusion criteria were pregnant women without PPRM, baby birth weight > 2500 gram, born in congenital abnormality, still birth, and referred to other hospitals before one day of age. The samples were collected consecutively.

This study had obtained ethical clearance from the Committee of Medical Research Ethics Dr. Cipto Mangunkusumo and Persahabatan Hospital, Jakarta and all subjects data were confidentially guaranteed before joined this study. The subject data were identified from medical records, including age, education levels, employment status, number of gravidas, gestational age, and baby birth weight. The maternal and umbilical cord vitamin D levels, CRP, IT ratio, and diagnosis of neonatal sepsis was collected by medical records. Data were analyzed by bivariate tests using independent T-test and Mann Whitney test.

## RESULTS

There were 72 patients take part the study. The average age of subjects was 28.50 years in a group with sepsis and 30.74 years in group without sepsis. Majority of subjects in both groups had length of study  $\leq$  12 years, 17 (77.3%) and 40 (80.0%) subjects, respectively. Most of the subjects were unemployed and became a housewife, there were 18 (82.0%) in group with sepsis and 36 (72.0) in another group. Based on number of gravidas, it was the first pregnancy for a half of subjects. In group with sepsis majority of subjects (11; 50.0%) had gestational age between 30-32 weeks while in group without sepsis majority (28; 56.0%) had gestational age between 32-34 weeks. The average of baby's birth weight was 1609 (1090-2310) grams in group with sepsis and 1824 (1015-2300) grams in group without sepsis. The characteristics of the subjects are presented in table 1.

**Table 1.** Subject's Characteristics

Demographical and Clinical Characteristics	Suspected Sepsis (n = 22)	Without sepsis (n = 50)
Age (years)	28.50	30.74
<b>Education levels (n, %)</b>		
Length of study $\leq$ 12 years (elementary school, junior, and senior high school)	17 (77.3) 5 (22.7)	40 (80.0) 10 (20.0)
<b>Length of study &gt; 12 years (university or academy)</b>		
<b>Employment status (n, %)</b>		
Unemployed	18 (82.0)	36 (72.0)
Employed	4 (18.0)	14 (28.0)
<b>Number of gravida (n, %)</b>		
1	12 (55.0)	24 (48.0)
2	4 (18.0)	9 (18.0)
3	4 (18.0)	11 (22.0)
4	1 (4.5)	6 (12.0)
5	1 (4.5)	0 (0.0)
<b>Gestational age (n, %)</b>		
28-30 weeks	7 (31.8)	7 (14.0)
30-32 weeks	11 (50.0)	15 (30.0)
32-34 weeks	4 (18.2)	28 (56.0)
Baby's birth weight (gram)	1609 (1090 – 2310)	1824 (1015 – 2300)

### Relationship between Vitamin D Levels of Maternal and Umbilical Cord with Early-onset Neonatal Sepsis Suspected

This study reported that the average of maternal vitamin D levels are 18.88 ng/ml (5.84-55.60 ng/ml) in EONS-suspected group and 28.18 ng/ml (8.25-63.49 ng/ml) in not EONS-suspected group. There were statistically differences between both groups. The relative risk (RR) value in this group were 0.96 (95% CI 0.93-0.99). These results showed that every 1 unit increase of maternal vitamin D level will reduce risk of EONS by 4% (1-7 %).

Based on vitamin D levels of umbilical cord, the average of vitamin D levels were 11.24 ng/ml (6.12-37.29 ng/ml) in EONS-suspected group and 14.81 ng/ml (4.47-53.35 ng/ml) in not EONS-suspected group. There were significant differences between both of groups. The RR value in this group were 0.95 (95% CI 0.89-1.00). These results showed that every 1 unit increase of umbilical cord vitamin D level will reduce risk of EONS by 5% (0-11 %).

**Table 2.** Relationship between Vitamin D Levels of Maternal and Umbilical Cord with Early-onset Neonatal Sepsis

Vitamin D levels	EONS-suspected (n, %)	Not EONS-suspected (n, %)	P-value	RR (95% CI)
Maternal vitamin D levels <sup>a</sup>	18.88 (5.84-55.60)	28.18 (8.25-63.49)	0.013 <sup>1</sup>	0.96 (0.93-0.99) <sup>2</sup>
Umbilical cord vitamin D levels <sup>a</sup>	11.24 (6.12-37.29)	14.81 (4.47-53.35)	0.024 <sup>1</sup>	0.95 (0.89-1.00) <sup>2</sup>

Description: <sup>a</sup>Expressed in the median (min-max); <sup>1</sup>Statistical test using the Mann-Whitney test; <sup>2</sup>RR values based on cox regression

If vitamin D levels were categorized as normal and low, this study showed that there was a significantly association between maternal vitamin D levels with EONS-suspected. Subjects with low maternal vitamin D levels had risk factor

1.48 times (1.12-1.95) to have baby with EONS higher than subject with normal maternal vitamin D levels. This study also reported that there was no association between umbilical cord vitamin D level with EONS.

**Table 3.** Relationship between Vitamin D Levels of Maternal and Umbilical Cord with Early-Onset Neonatal Sepsis (categorical)

Vitamin D levels	EONS-suspected n (%)	Not EONS-suspected n (%)	P-value	RR (95% CI)
Maternal vitamin D levels				Reference
Normal	3 (13.6)	22 (44.0)	0.013 <sup>1</sup>	1.48 (1.12 – 1.95)
Low	19 (86.4)	28 (56.0)		
Umbilical cord vitamin D levels				Reference
Normal	1 (4.5)	8 (16.0)	0.259 <sup>2</sup>	1.33 (0.99 – 1.78)
Low	21 (95.5)	42 (84.0)		

Description: <sup>1</sup>Statistical test using Chi-square test, <sup>2</sup>Statistical test using Fisher-exact test

## DISCUSSION

Neonatal sepsis was systemic infection characterized by clinical manifestation of infection with port entry of microbes. Neonatal sepsis was one of the most common cause of neonatal mortality and morbidity both in developing and developed countries.

A cross-sectional study at the tertiary Obstetrics and Gynecology center in Kosovo. The study involved 200 pregnant women with PROM and newborns. Overall, 13% of newborns had early-onset neonatal infections, and sepsis was

evident in 5% of cases.<sup>8</sup>

In this study from total of 72 subjects with preterm premature of membrane (PPROM), there were 22 (31%) early-onset neonatal sepsis (EONS)-suspected newborns while 50 (69%) newborns were not EONS-suspected. These results were higher than in other studies. in Tertiary Obstetrics and Gynecology Center in Kosovo. From total of 200 pregnant women with PPRM, 13% newborns had early-onset neonatal infection and 5% were proved to have neonatal sepsis.<sup>9</sup>

This study showed that maternal vitamin D levels were significant differences between EONS-suspected group and not EONS-suspected group. Every 1 unit increase of maternal vitamin D level will reduce risk of EONS by 4% (1-7 %). If maternal vitamin D levels were classified as normal and less than normal, there was an association between maternal vitamin D levels and EONS. Maternal vitamin D levels less than normal had risk 1.48 times (95% CI 1.12-1.95) to had EONS than maternal with normal vitamin D levels. These results were similar to a study conducted by Muhammad Tariq Nadeem<sup>10</sup> which reported low maternal vitamin D levels is significantly associated with low serum neonatal vitamin D levels and higher risk of EONS. From total of 93 neonates who had neonatal sepsis and 93 neonates born without sepsis as controls, deficiency of vitamin D was found in 88.17% maternal sample and 82.80% neonatal sample who had neonatal sepsis.

Reported 100 neonates in Neonatal Intensive Care Unit in Sultan Suleyman Hospital Turkey in 2012. Total of 50 term babies with clinical signs of infection and 50 term babies without clinical signs of infection were taken for blood collecting to measure 25-hydroxyvitamin D (25-OHD) during first 3 postnatal days. Vitamin D was a prohormone while the main form of vitamin D circulated in blood vessels was 25-OHD. These molecules were specifically bound to plasma carrier proteins which carry vitamin D and calcitriol.<sup>11-13</sup>

Vitamin D deficiency in circulation played role in the pathogenesis of infection. Vitamin D receptors were expressed in all of the ligands cellular immunity subsets by 25-OHD then triggered native immune cells such as monocyte, macrophage, and neutrophil to increased chemotactic, phagocytic, and bactericide activity. This activity caused conversion of 25-OHD<sub>3</sub> (calcidiol) to active form 1,25-OH<sub>3</sub> (calcitriol). Calcitriol was secosteroid hormone which bind vitamin D receptors to release signals in the tissue and cell so finally induced production of antimicrobe peptide such as cathelicidin, delayed Gram-positive and Gram-negative bacteria colonization. Complex vitamin D receptors directly induced antimicrobe protein expression such as  $\beta$ -defensin or cathelicidin in the native immune cells.<sup>5,14</sup> Cathelicidin and  $\beta$ -defensin had

wide antimicrobe activity to certain virus and fungi. The role of vitamin D caused increase of cathelicidin 10 times.<sup>15</sup>

In this study, the average vitamin D levels of umbilical cord were significantly difference between EONS-suspected group (11.24 ng/ml) and not EONS-suspected group (14.81 ng/ml). Every 1 unit increase of maternal vitamin D level will reduce risk of EONS by 5% (0-11 %). It was similar from total of 100 preterm neonates with gestational age <37 weeks, 63% had vitamin D deficiency ( $\leq 5$  ng/ml), 24% had vitamin D insufficiency (5-15 ng/ml), and 13% had lack of vitamin D ( $>15$  ng/ml).<sup>16</sup> Incidence rate of sepsis increased in vitamin D insufficiency group. In this study, we concluded that lack of vitamin D that detected in blood circulation taken by umbilical cord and associated with neonatal sepsis levels in preterm neonates. This result showed that lack of vitamin D was one of risk factors of sepsis in preterm neonates and there was an association between vitamin D levels of the umbilical cord and neonatal sepsis in preterm newborns. However, if vitamin D levels of the umbilical cord was classified as normal and abnormal (insufficiency and deficiency), there was no significant association between vitamin D levels of umbilical cord and EONS.

## CONCLUSION

Maternal and umbilical cord vitamin D levels was significantly associated with EONS in premature newborns.

## REFERENCES

1. Indonesia HTA. Prediksi Persalinan Preterm. Kementerian Kesehatan Republik Indonesia. 2007.
2. Chandranita M. Pengantar Kuliah Obstetri. EGC. 2007:925.
3. Mukhopadhyay S. Risk Assessment in Neonatal Early Onset Sepsis. Elsevier, Sem Perinatol. 2012;408:15.
4. Indonesia KKR. Profil kesehatan Indonesia. Ind. 2017;351:77.
5. Badan Penelitian dan Pengembangan Kesehatan DK, Republik Indonesia. Riset Kesehatan Dasar. 2007.
6. Damarati dan Yulis P. Analisis Tentang Paritas Dengan Kejadian Ketuban Pecah Dini pada Ibu Bersalin Di RSUD Sidoarjo. J Keb. 2012:1.
7. Saira Dars SM. Maternal morbidity and perinatal outcome in preterm premature rupture of membranes before 37 weeks gestation. Pak J Med Sci. 2014;30(3):626-9.

8. Ibishi VA, Isjanovska, R., & Malin, A. E. Early-onset neonatal infection in pregnancies with prelabor rupture of membranes in Kosovo: A major challenge. *Turk J Obstet Gynecol.* 2018;15(3):171-6.
9. Saraswati DD PA. Faktor risiko yang berperan pada mortalitas sepsis. Departemen Ilmu Kesehatan Anak Fakultas Kedokteran Universitas Indonesia, Rumah Sakit Cipto Mangunkusumo, Jakarta, Sari Pediatri. 2014;281:8.
10. Muhammad Tariq Nadeem FA, Mubashra Samina. Lower Maternal Vitamin-D Levels' Association With Early-Onset Neonatal Sepsis In Term Neonates. *Pak Armed Forces Med J.* 2018;68(856):62.
11. M Cetinkaya FC, G Buyukkale. Lower vitamin D levels are associated with increased risk of early-onset neonatal sepsis in term infants. *J Perinatol.* 2015;35(39):45.
12. Rech MA HT, Rodriguez J. Deficiency in 25-hydroxyvitamin D and 30-day mortality in patients with severe sepsis and septic shock. *AJCC.* 2014;23(9): 71-9.
13. Speeckaert M HG, Delanghe JR, Taes YE. Biological and clinical aspects of the vitamin D binding protein (Gc-globulin) and its polymorphism. *Clin Chim Acta.* 2006;372(33):42.
14. Gamal Taha, Madiha Abd-Allah, Hanan Mostafa, Abdel-Azeem Mohamed, Marian Gamil. Neonatal and Maternal 25-OH Vitamin D Serum Levels in Neonates with Early-Onset Sepsis. *Pediatric Departement, El-Minya University, Minya, Egypt.* 2017;4(5):37.
15. Sri Utami AC, Kusnandi RI. Perbandingan Kadar Vitamin D (25 Hidroksivitamin D) pada Anak Sakit Kritis dan Nonkritis, Departemen Ilmu kesehatan Anak Fakultas Kedokteran Universitas Padjadjaran/Rumah Sakit Hasan Sadikin, Bandung. *Sari Pediatri.* 2015;16.
16. Birgul Say NU, et all. Effects of cord blood vitamin D levels on the risk of neonatal sepsis in premature infants. Division of Neonatology, Zekai Tahir Burak Maternity Teaching Hospital, Ankara, Turkey, Korean. *J Pediatr* 2017;60(8):248-53.