Annals of Neonatology

OPEN ACCESS
ISSN: 2636-3596

Original Article

Role of Vitamin D and Parathyroid Hormone Levels in Prediction of Late Onset Sepsis among Preterm Infants: A Prospective Cohort study

Noura M.Ibrahim Elbakry*[1]; Ayat Mostafa Mohamed[2]; Ahmed N. Gamil[1]
DOI: 10.21608/ANJ.2024.276513.1087
***Correspondence** Pediatric Department, Faculty of Medicine, Minia University, Egypt
Email: nourabakry@gmail.com
Full list of author information is available at the end of the article

Abstract

Background: Preterm infants (PTs) have a higher risk for vitamin D insufficiency, which is associated with a higher morbidities & mortality. Decreased vitamin D level in blood plays a role in sepsis because vitamin- D-related pathways are associated with many immunological and endocrine functions and also Vitamin D is an important for immune system development. **Aim**: To demonstrate the association between vitamin D level and occurrence of late onset sepsis (LOS) in PTs. **Methods**: This is a case-control study included preterm babies who were admitted to Minia University Hospital's Neonatal Intensive Care Unit (NICU). Study groups were included; Group I of sixty five PTs≤30-32 weeks of gestational age (GA) and/or≤1500g birth at 28 days of age and this group of preterm babies were subdivided into two subgroups at follow up at one month of age into Group Ia with low vitamin D baseline < 20 ng/ml, Group Ib with vitamin D baseline > 20 ng/ml on follow up at one month of life. While group II include 50 full term babies >32weeks of gestational age (GA) and/or>1500g birth at 28 days of age healthy ones served as control. **Results**: The PTs with vitamin D deficiency showed a higher incidence of LOS and correlation was observed between incidence of LONS(r: - 0.16 p: 0.0001), length of hospital stay (r: 0-.77; p: 0.001) with vitamin D levels in neonates especially preterm ones. **Conclusion**: Preterm neonates with low vitamin D levels are more likely to develop sepsis with more disease severity, higher mortality, and higher duration of hospital admission also, a percentage of critically ill neonates have vitamin D deficiency.

Keywords: Vitamin-D, preterm infants, low weight, late sepsis, parathyroid

Introduction

Neonatal sepsis is a clinical syndrome of systemic illness accompanied by bacteremia occurring in the first month of life. [1-3]

Neonatal sepsis is a medical entity affecting infants under 28 days of age with signs of systemic infection and isolated infections in the bloodstream.[4]

Sepsis in neonates have an incidence of 1-7/1000 live births and 12-27/1000 live births for infants < 1500g and mortality is 13-25%.[4] and increased rates in premature neonates classified as severe sepsis when it is associated with organ dysfunction.[5]

Sepsis is divided into two types ;Early onset sepsis(EONS) which develops in the 1st week of life but it is sometimes restricted to the first three days of postnatal life ,usually multisystem disease with severe respiratory symptoms and high mortality rate.[6]Early onset sepsis acquired from genital tract intrapartum and usually associated with chorioamnionitis.[7] while late onset sepsis occur as early as five days but it is most common after the first week of life and less association with obstetric complications,[8,9] and usually have a known cause , often meningitis or sepsis and its usually acquired from the environment, *Staphylococci* account for 30 to 60% of LONS cases and are due to intravascular devices (particularly central vascular catheters). [11,12]

E.coli is also a significant cause of late-onset sepsis, especially in extremely preterm infants.[13,14] Neonatal sepsis is diagnosed by poor suckling, skin mottling and respiratory distress, laboratory markers as elevated C- reactive protein(CRP) , positive blood cultures for E. Coli and Staphylococci or other organisms. [23-25], also contaminated ryle tubes may be a cause for introduction of organinsms. [26] While contaminated respiratory equipment is suspected in outbreaks of hospital- acquired *Pseudomonas* pneumonia among preterms. [27] Although screening and intrapartum antibiotic prophylaxis for group B streptococcus have significantly lowered the rate of early-onset sepsis due to this

organism, the rate of late-onset GBS sepsis has remained unchanged, which is consistent with the hypothesis that LONS is usually acquired from the environment. [28] The role of anaerobes as *Bacteroides fragilis* in LONS in preterm infants remains unclear, although deaths among preterms were due to *Bacteroides* bacteremia. [29] Also candida species are important causes of LONS, occurring in 10 to 18% of preterms. [30]

Vitamin D is an essential for neonate's especially preterm ones it is important for calcium &phosphate metabolism, for immunity, endothelial function, and antimicrobial activity [14]. Immune system cells express vitamin D receptors (VDRs), vitamin D is essential for immune system regulation [15]. It regulates the balance between inflammation and tissue damage by promoting lymphocyte differentiation. [16] Vitamin D decrease the production of cytokines as interleukin (IL)-2, IL-6, IL-8, and tumor necrosis factor-α (TNF-α). [17] Also the immune cells including monocytes and antigen-presenting cells (APCs), express vitamin D receptors. [18]

Vitamin D promotes the transition in the immune system from helper T (Th1) and Th17 to Th2 and regulatory T cells. [19] Vitamin D also improves intestinal health and homeostasis by decreasing intestinal damage by lipopolysaccharide (LPS). [20]

Vitamin D deficiency in preterm infants can weaken the immune system, alter hormonal metabolism, and cause the spread of various diseases, infections, and serious illnesses all of which can be fatal.

Patients and Methods

This Prospective Cohort study conducted at NICU(neonatal intensive care unit) in Minia University Hospitals onto Sixty five preterms≤30-32 weeks' GA and/or≤1500 g birth weight (Group I) with inclusion criteria and other fifty term healthy babies represent(Group II)with measured vitamin D serum levels at birth. Babies were excluded if they did not matches the age and weight at birth established, also if mortality before 36 weeks, Chromosomel

abnormalities, Genetic anomalies or Congenital malformations. We carried out a follow-up on infants at one month and grouped into two subgroups for tests of association with clinical outcomes based on vitamin D blood levels: Group Ia with low vitamin D Baseline < 20 ng/ml , Group Ib with vitamin D Baseline > 20 ng/ml, according to the criteria of the Endocrine Society Clinical Practice Guidelines.[18]

Collection of data and definitions:

Demographic data, including data on pregnancy and delivery were collected from the mothers. All preterm neonates newly diagnosed with LONS between Feburary 2024 and May 2024 participated in this study. Diseases of prematurity were noted: sepsis, hyaline membrane disease, bronchopulmonary dysplasia (BPD), intraventricular hemorrhage, periventricular leukomalacia, retinopathy of prematurity and necrotizing enterocolitis (NEC). [35] Late onset sepsis (LOS) is defined as occurance of signs and symptoms of severe sepsis after three days of life. [42-45].

Methodology:

Blood sampling protocol: venous blood samples obtained from neonates under complete aseptic condition at 28 days of life and at one month for the following routine and specific investigation ,include Blood culture done using (BD™ BACTEC™ FX40 Automated Blood Culture System, Becton Dickinson, USA) and subcultures done for positive cases to identify the causative organism [identification and AST done by (VITEK-2, bioMérieux -France)]. Complete blood count, with differential determined by automated cell counter, Sysmex KX-21N (TAO Medical incorporation, Japan). Separated sera were used for measuring CRP by kinetic method (by GENRUI,Biotec Inc.in china.),according to the manufactures instruction.The remaining serum was preserved at -80°c until determination of serum level of vitamin D and parathyroid hormone(PTH) by fully automated Chemiluminescence technology (cobas E 411-Roche Diagnostic GmbH Germany). Serum calcium and

phosphorus were assessed by (Mindray-BS-800M, China).

Ethical consent

Ethics approval: The ethics committee for the faculty of medicine authorized this research. Our study was carried out in accordance with the Declaration of Helsinki and approved by the Institutional Hospital Ethical Committee number 1059-01-2024. Participants Informed written consent was obtained from their parents or legal guardians. Maintain the participant's privacy and anonymity, avoiding the use of misleading tactics, allowing participants to leave our study at any time, a release for publishing was obtained.

Availability of data and materials: The corresponding author may be reached for a reasonable request for the datasets utilized and/or analyzed in the present work.

Statistical Analysis:

Data were collected, tabulated and statistically analyzed using an IBM compatible personal computer with Statistical Package for the Social Sciences (SPSS) version 26 (SPSS Inc. Released 2018. IBM SPSS statistics for windows, version 26.0, Armnok, NY: IBM Corp.) non-numerical data were given as percentages, whereas numerical variables were expressed as means and standard deviations. Using two-tailed t-tests, the variations between both groupswere calculated. P-values below 0.05 were regarded as significant. The correlation coefficient of Pearson determined the magnitude of correlations. Using the statistical software Prism 3.0, all data were evaluated (Graph Pad Software, USA: San Diego, CA). Microsoft Office Excel 2016 was utilized to calculate the numbers.

Results

Regarding demographic data of groups, there were no differences observed between the control group and the PTs group in relation to the age of the mothers and sex of infants. Table 1

Regarding biochemical data of groups there were no differences in vitamin D serum

levels at birth when comparing PTs to term infants, or regarding maternal levels. Table 2

There was a positive correlation regarding vitamin D serum levels of mother/ infant (r: 0.466; p < 0.001) in both groups. Regarding the biochemical data analyzed; increased levels of PTH were observed in the PTs group. We found differences in the levels of calcium and phosphorus among groups; such did not have clinical relevance as values were still within the normal range. Table 2

A comparative analysis was conducted to identify factors associated with vitamin levels at birth and we found that vitamin D levels were dependent on the mother's levels. Considering a cut-off point of 20 ng/ml for 25(OH) D, PTs (%) had vitamin D serum levels < 20 ng/ml and PTs (%) had vitamin D levels > 20 ng/ml. Table 3

The most frequent co-morbidities in preterm babes were LOS (48%), when the two subgroups of PTs were arranged according to Vitamin D and PTH levels (vitaminD<20ng/ml and PTH>60pg/ml versus vitamin D>20ng/ml and PTH<60pg/ml). Table 2

At one month of age; Group Ia with low was 49 babies while 16 infants were in group Ib with vitamin D Baseline > 20 ng/ml, the incidence of LOS was higher in the subgroup with low vitamin D levels <20 and PTH>60 Table 3

We demonstrated that vitamin D levels at one month of age were independently associated with LOS (P <0.025). Table 3 In preterm groups with low vitamin D show sepsis markers as positive CRP more than 6 mg/dl, high total white blood cell count, positive blood cuture (for staphaloccoci, E.Coli &for other organisms) Table 4

No correlation was observed between levels of PTH (r: 0.065; p: 0.545), calcium (r: 0.024; p: 0.816), or phosphorus (r: - 0.039; p: 0.721) with vitamin D. Table 5

Correlation was observed between incidence of LONS (r: - 0.16 p: 0.001), length of hospital stay (r: 0-.77; p: 0.001) with vitamin D. Table 5.

The receiver-operating characteristic (ROC) curve for serum vitamin D as a predictor of LONS, it shows an area under the curve (AUC) of 0.82 with sensitivity of 78.1% and specificity of 61.4% at cut off value for serum vitamin D of < 20.5 ng/ml (Figure 1).

Table 1: Demographic Data of Groups

Variables	**Group I Preterm infants N=65**	**Group II Term infants N=50**	**p-value**
Gestational age (weeks)	29.9±2.4	38.7±1.14	< 0.05
Birth weight (gr)	1311±307	3294±528	< 0.05
Length (cm)	38.8±3.5	49.7±3	< 0.05
Sex(male)	24 (49%)	20(40%)	0.34

Table 2: Biochemical Markers in Prematurity and Term Infants

Variables	**Group I Preterm infants N=65**	**Group II Term infants N=50**	**p-value**
Vitamin D levels in Mothers (ng/mL) (mean± SD)	10.49 (22.15)	9.78 (24.20)	0.345
Vitamin D levels in Neonates (ng/mL) (mean± SD)	18.6 (13.62)	13.2 (7,85)	0.254
Calcium (mg/dl) (mean± SD)	10.15(7.4)	11(6)	< 0.05
Phosphorus (ng/ml) (mean± SD)	5.5 (9.3)	6.2 (8.1)	< 0.05
PTH (pg/mL) (mean± SD)	49.1(84.68)	2.25 (3.55)	< 0.05

PTH: Parathyroid hormone.

Table 3: Characteristics of Preterm Infants According to Vitamin D Levels at One Month of Age

Item	Group Ia vitamin D Baseline < 20 ng/ml N=49	Group Ib vitamin D Baseline > 20 ng/ml N= 16	p-value
Sex(male)	38	10	0.311
Gestational age (weeks)	29.57±2.51	30.48±2.08	0.357
Birth weight (gr)	1197±267.6	1435.16±294.32	< 0.05
Breastmilk feeding	9	10	0.323
Mechanical ventilation	15	10	0.305
Parenteral nutrition/central catheter exposure (days)	17 (8)	10 (4)	< 0.05
Days of NICU admission	48	36	< 0.05
Mothers vitamin D levels(ng/mL)	9.78	10.49	0.345
Mean Vitamin D levels in infants (ng/mL)	13.2	22.6	0.254
Mean Calcium level (mg/dl)	11	10.15	< 0.05
Mean Phosphorus level (ng/ml)	6.2	5.5	< 0.05
Mean PTH level (pg/mL)	2.25	49.1	< 0.05

PTH; parathyroid hormone

Table 4: Characteristics of Preterm Infants According to Late Onset Sepsis Markers at One Month of Age

Item	Group Ia vitamin D Baseline < 20 ng/ml N=49	Group Ib vitamin D Baseline > 20 ng/ml N= 16	P –value
CRP (mg/dl)(mean± SD)	6.5-24.5 12.73±30.76	0.20-0.60 0.38±0.11	0.0001
Total white blood cell count (mean± SD)	7-21 17.42±1.62	2.90-4.5 1.86±0.43	0.001
Positive blood culture for staphylococcus (%)	16 (32.6%)	0.00	0.001
Positive blood culture for E.Coli (%)	17(34.7%)	0.00	0.0001
Positive blood culture for other organisms (%)	16(32.6%)	0.00	0.0001

Table 5: Different Correlations with Vitamin D Level

Item	Vitamin D(ng/mL)	
	R	P- Value
Serum calcium(mg/dl)	0.024	0.816
Serum PTH(pg/mL)	0.065	0.545
Serum phosphorous(ng/ml)	0.039	0.721
Late onset sepsis incidence (%)	-0.16	0.001
Hospital stay(days)	-0.77	0.001

PTH; parathyroid hormone

Discussion

Late onset neonatal sepsis in preterm infants was associated with low vitamin D levels, below 20 ng/mL in cord blood because these levels are associated by abnormal monocyte responses that make newborns more vulnerable to infections. [42-45]

Regarding demographic data of our study groups there were no differences observed between the full term infants and the PTs group in relation to the age of the mothers and sex of infants also for biochemical data of groups there were no differences in vitamin D levels at birth when comparing PTs to term infants, or regarding maternal levels. We found a positive correlation for vitamin D serum levels of mother/ infant (r: 0.466; $p < 0.001$) in both groups and we found that vitamin D levels were dependent on the mother's levels.

Cariolou M, et al.(2019)studies have described that maternal vitamin D serum levels < 20 ng/mL is a risk factor for neonatal poor outcomes,also suggested that pregnant females should have vitamin D serum levels > 35 ng/mL for good maternal and neonatal outcomes.[43]

Our results showed that in PTs, higher PTH levels at birth and these did not reach a normal range until one month of age, also this was in agreement with study of Cariolou M ,et al.,(2019) that indicate the vitamin D levels only does not define its deficiency or normal state and that the vitamin D-PTH relationship

must be cosidered as PTH is a major hormone of bone resorption, and its serum levels are indicator for secondary hyperparathyroidism and metabolic bone disorders in extremely low birth weight neonates and preterms.[44,45]

We found differences in the levels of calcium and phosphorus among the term and preterm; such did not have clinical relevance as values were still within the normal range also there was no correlation between calcium (r: 0.024; p: 0.816) or phosphorus (r: -0.039; p: 0.721) levels and vitamin D. LOS incidence varies between 20% to 38% with PT in the first 120 days of life[45] while the high prevalence of LOS in our study population (48%) may be due to the choice of PT who is more risk for infections due immature immune system. [45]

We carried out a follow-up on infants at one month and classed them into two subgroups for tests of association with clinical outcomes based on vitamin D blood levels; Group Ia with low vitamin D Baseline < 20 ng/ml and there were forty nine babies while Group Ib with vitamin D baseline > 20 ng/ml were sixteen ones Analysis of our results after 1 month showed that decreaed vitamin D and high PTH levels were associated with more LOS levels in PT and this in agree with the research of Mao Zedong, etal., (2018) reported more vitamin D deficiency in critical illness in preterm infants such as hyaline membrane disease, NEC, patent ductus arteriosus, and sepsis which are common in PT in the first days of life. Therefore, PTs admitted to the NICU are at higher risk for vitamin D deficiency. [45]

Laboratory markers for sepsis as high CRP ,leucocytosis and postive blood cultures were reported and incidence of LOS after 1 month of observation was higher in the group with low vitamin D level and we showed that vitamin D at one month of age was independently associated with LOS (P< 0.025) and did

not affect the rate of breastfeeding and the different exposures to ventilators while In study reported by Çetinkaya M et al. (2015), it was found that the lower the blood concentration of vitamin D, the higher the risk of EOS. [46] also Çetinkaya M et al. (2015) reported that pregnant women and their babies should reach higher vitamin D levels to prevent poor outcomes, and that vitamin D deficiency increases the risk of abortions and EOS and recommended measuring levels during pregnancy. [46] While, in another study, Hollis BW (2005) discovered that preterm with EONS had significantly lower vitamin D concentrations as well as discovered a positive correlation between vitamin D and high CRP, TNF-α, and IL-6 [38]. longer hospital stays in our study for PTs who developed sepsis was associated with delayed advances of enteral feeding in this group and also correlation was observed between incidence of LONS(r: - 0.16 p: 0.0001), length of hospital stay (r: 0-.77; p:0.001) with vitamin D levels in neonates especially preterm ones, and this is consistent with the study of Gäddnäs FP et al. (2020) determined total central vein catheter exposure and parenteral nutrition days as risk factors for sepsis and stated that breastfeeding is protective. [46]

In contrast to our results, study of WorknehBitew Z, etal., (2020) sepsis markers such as positive CRP, total white blood count and positive blood count were higher in the l full term infants with critical illness ($p < 0.05$) and reported decreased vitamin D levels in their mothers and stated that there is a positive relationship between vitamin D concentrations in infants and parents. [35] Our results showed that serum vitamin D as a predictor of LONS has a sensitivity of 78.1% and specificity of 61.4% at cut off value for serum vitamin D of < 20.5 ng/ml,While Jones T, et al.(2010)found that the ROC curve of specificity and sensitivity of vitamin D in the prediction of early onset sepsis

(EONS), the sensitivity was 100%, the specificity was 73%, the positive predictive value was 73 at a vitamin D cut-off value of 20 ng/mL.[47,48]

Results have been reported by Tayel S, et al. (2018) in this point,It is important to establish the optimal dose of vitamin D intake among hospitalized PTs to achieve adequate vitamin D levels and prevent adverse outcomes. [8]

Limitation: limitations of the present study include small sample size

Conclusions

Preterm infants who have vitamin D deficiency with levels < 20 ng/ml have an increased chance of developing LONS and more severe outcomes.

Abbreviations

Antigen-presenting cells: (APCs), bronchopulmonary dysplasia: (BPD), C-reactive protein: (CRP), early-onset neonatal sepsis: (EONS), gestational age: (GA), lipopolysaccharide: (LPS), late-onset neonatal sepsis: (LONS), Preterm infants: (PTs) Radioimmunoassay: (RIA), T helper: (Th), Tumor necrosis factor-alpha: (TNF-α), interleukin: (IL), necrotizing enterocolitis: (NEC), neonatal intensive care unit: (NICU), Parathyroid hormone: (PTH), vitamin D receptors: (VDRs).

Acknowledgements:

We would like to thank all medical staff at NICU of Minia university hospital for their support.

Competing interests

The authors declare that no conflict of interest

Funding

No funding agency is providing us with assistance for this project in the form of funds.

Authors' contributions

NE and AG: Study design and analysis, interpretation of data, drafting of the manuscript and revision of the manuscript for important intellectual content. AM: laboratory data interpretations and Statistical analysis. All the authors reviewed and approved the final manuscript; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Author's details

[1]Pediatric Department, Faculty of Medicine, Minia University, Egypt

[2]Clinical-pathology Department, Faculty of Medicine, Minia University, Egypt

Date received: 17th May 2024, accepted 30th June 2024

References

1. Kołodziejczyk Nowotarska A, Renata Bokiniec R, Seliga-Siwecka J. Monitored supplementation of vitamin D in PTs: a randomized controlled trial.Nutrients. 2021; 13:34-42.
2. Kheiri B, Abdalla A, Osman M, Ahmed S, Hassan M, Bachuwa G.Vitamin D deficiency and risk of cardiovascular diseases: a narrative review. Clinical Hypertent. 2018; 24:9-11.
3. Eman M. Alissa, Wafa a Alnahdi, Nabil Alama,insulin resistance in Saudi postmenopausal women with and without metabolic syndrome and its association with vitamin D deficiency. J Clin Transl Endocrinol. 2014; 2:42–7.
4. Douros K, Boutopoulou B, Fouzas S, Loukou I. Asthma and allergy "epidemic" and the role of vitamin D deficiency. Adv Exp Med Biol. 2017; 996:169–83.
5. Melguizo-Rodríguez RI-ML, Ruiz C. Víctor J Costela-Ruiz.vitamin D and autoimmune diseases. Life Sci. 2019; 233:246.
6. Goyal H, AbhilashPerisetti M, Rahman R, Levin A, Lippi G. Vitamin D and gastrointestinal cancers: a narrative review. Dig Dis Sci. 2019; 64:10-98.
7. Adams J, Hewson M. Unexpected actions of vitamin D: new perspectives on the regulation of innate and adaptive immunity. Nat Clin Pract Endocrinol Metab. 2018; 4:80– 90.
8. Tayel S, Soliman S, Elsayed H. Vitamin D deficiency and vitamin D receptor variants in mother and their neonates are risk factors for neonatal sepsis. Steroids. 2018; 134:37–42.
9. Quaraishi S, De Pascale G, Needleman JS, Nakazawa H, Kaneki M, Bajwa E. Effect of cholecalciferol supplementation on vitamin D status and cathelicidin levels in sepsis: a randomized, placebo- controlled trial. Crit Care Med. 2015; 43:1928–37.
10. Clancy N, Onwuneme C, Carrol A, McCarthy R, McKenna MJ, MurphyN.Vitamin D and neonatal immune function. J Matern Fetal Neonatal Med. 2013; 26:639–46.
11. Meng N, Qianqian Z, Jiuru Z, Qianwen S, Dongting Y, Tao W. Relationship between maternal vitamin D status in the first trimester and neonatal outcomes: a retrospective single center study. BMC Pediatr.2021; 21:-330.
12. Ch KB. Vitamin d supplementation in the ICU patient. Vitamin D supplementation

in the ICU. Curr Opin Clin Nutr Metab Care.2015;18: 187.

13. Bansal S, Kaur A, Rai S, Kaur G, Goyal G, Singh J. Correlation of vitamin D deficiency with predictors of mortality in critically ill children at a tertiary Care Centre in North India-a Prospective. Observational Study.JPediatr Intensive Care. 2020; 11:54–61.
14. He M, Cao T, Wang J, Wang C, Wang Z, Abdelrahim MEA. Vitamin D deficiency relation to sepsis, paediatric risk of mortality III score, need for ventilation support, length of hospital stay, and duration of mechanical ventilation in critically ill children: a meta-analysis. Int J ClinPract. 2021;75: 139-48.
15. Amrein K, Litonjua AA, Moromizato T, Quraishi SA, Gibbons FK, Pieber TR. Increases in pre-hospitalization serum 25(OH) D concentrations are associated with improved 30-day mortality after hospital admission: a cohort study. ClinNutr. 2016; 35:51-4.
16. Dall`Agnola A, Beghini L. Post-discharge supplementation of vitamins and minerals for preterm neonates. Early Hum Dev. 2009; 85:27–9.
17. Martínez Suárez V, Moreno Villares JM, Dalmau Serra J, de Nutrición C.Recommended intake of calcium and vitamin D: positioning of the nutrition committee of the AEP.AnPediatr. 2012;77(57):1–8.
18. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA,HeaneyR.Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J ClinEndocrinolMetab. 2011; 96:19-21.
19. Wagner CL, Greer FR.American Academy of Pediatrics Committee on Nutrition. Prevention of rickets and vitamin D deficiency in infants, children and adolescents. Pediatrics. 2018;122: 14-22
20. Pérez-Castillo IM, Rivero-Blanco T, León-Ríos XA, Expósito-Ruiz M,López-Criado MS, Aguilar-Cordero MJ. Associations of vitamin D deficiency, parathyroid hormone, calcium, and phosphorus with perinatal adverse outcomes. A Prospective Cohort Stud Nutrients. 2020; 12:32-79.
21. Sachan A, Gupta R, Das V, Agarwal A, Awasthin P, Bhatia V. High prevalence of vitamin D deficiency among pregnant women and their newborns in Nothern India. Am J ClinNutr. 2005; 81:10-60.
22. Vanlaere I, Libert C. Matrix metalloproteinases as drug targets in

infections caused by gram-negative bacteria and in septic shock. ClinMicrobiol Rev. 2019; 22:224–38

23. Cena J, Lalu MM, Rosenfelt C, Schulz R. Endothelial dependence of matrix metalloproteinase-mediated vascular hyporeactivity caused by lipopolysaccharide. Eur J Pharmacol. 2018; 582:11-16.
24. Rosendahl J, Holmlund-Suila E, Helve O, Viljakainen H, Hauta-AlusH,Valkama S. 25-hydroxyvitamin D correlates with inflammatory markers in cord blood of healthy newborns. Pediatr Res. 2017; 81:731–5.
25. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2011
26. Stocker M, van Herk W, El Helou S, Dutta S, SchuermanF, van den T.C- reactive protein, Procalcitonin, and white blood count to rule out neonatal early- onset Sepsis within 36 hours: a secondary analysis of the neonatal Procalcitonin intervention study. Clin Infect Dis. 2021;15(73): 383–90.
27. Tamblyn J, Pilarski N, Markland A, Marson EJ, Deall A, HewisonM.Vitamin D and miscarriage: a systematic review and meta-analysis. FetilSteril. 2022; 118:111–22
28. Andrews RE, Coe KL. Clinical presentation and multifactorial pathogenesis of necrotizing Enterocolitis in the preterm infant. Adv Neonatal Care.2021;21:349–55.
29. Agwu A, Neptune A, Voss C, Yenia B, Rustein R. Parathyroid hormone as a functional indicator of vitamin D sufficiency in children. JAMA Pediatr.2014;168:383–5.
30. Joung KE, Marter LV, McElrath TF, Michael Z, Tabatabai P, Litonjua A.Vitamin D and bronchopulmonary dysplasia in preterm infants. J Perinatol. 2016; 36:878–82.
31. Bozkaya A, Yurttutan S, Özkars MY, Doğaner A. Respiratory problems in preterm infants with pulmonary hemorrhage. J Matern Fetal Neonatal Med. 2021; 12:1–6.
32. BarnetteBW SBT, Armenta RF, Wynn JL, Richardson A, Sharma J. Contribution of concurrent comorbidities to Sepsis- related mortality in preterm infants ≤32 weeks of gestation at an academic neonatal intensive care network. Am J Perinatol. 2021; 14:21-33.
33. Starr R, De Jesus O, Shah SD, Borger J. Periventricular and intraventricular Hemorrhage. Stat Pearls [internet]. Treasure Island (FL): Stat Pearls Publishing; 2022; 16:23-44.
34. Amrein K, Scherkl M, Hoffmann M, Neuwersch-Sommeregger S, Kösten- berger M, Berisha A. Vitamin D deficiency an update on the current status worldwide. Eur

J ClinNutr. 2020; 74:14- 98

35. WorknehBitew Z, Worku T, Alemu A. Effects of vitamin D on neonatal sepsis: a systematic review and meta-analysis. Food SciNutr. 2020; 9:37-55.
36. McDonell SL, Baggerly KA, Baggerly CA, Aliano JL, French CB, BaggerlyLL.Maternal 25 OHD concentrations >40 ng/mL associated with 60% lower preterm birth risk among general obstetrical patients at an urban medical center. PLoS One. 2017; 12:22-3.
37. Martinez Suarez V, Dalmau SJ. Hypovitaminosis D. Pediatr Integr. 2020; 1:351–5.
38. Hollis BW. Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. J Nutr. 2005; 135:317–22
39. Agarwal A. Kovilam, Agrawal DK. Vitamin D and its impact on maternal fetal outcomes in pregnancy: a critical review. Crit Rev Food Sci Nutr.2018; 58:755–69.
40. Christoph P, Challande P, Raio L, Survek D.High prevalence of severevitamin D deficiency during the first trimester in pregnant women in Switzerland and its potential contributions to adverse outcomes in the pregnancy. Swiss Med Wkly. 2020; 28(150):202-38.
41. Specker B. Vitamin D requirements during pregnancy. Am J Clin Nutr.2014;80:17-40.
42. Bi WG, Nuyt AM, Weiler H, Leduc L, Santamaria C, Wei SQ. Association between vitamin D supplementation during pregnancy and offspring growth, morbidity, and mortality: a systematic review and Meta-analysis. JAMA Pediatr. 2018; 172:635–45
43. Sotunde OF, Laliberte A, Weiler HA. Maternal risk factors and newborn infant vitamin D status: a scoping literature review. Nutr Res. 2019; 63:1-19
44. Cariolou M, Cupp M, Evangelou E, Tzoulaki I, Berlanga-Taylo J.Importance of vitamin D in acute and critically ill children with subgroup analyses of sepsis and respiratory tract infections: a systematic review and metaanalysis. BMJ Open. 2019; 9(5):22-30.
45. Mao X, JieQiu LZ, JunjieXu JY, Yang Y. Vitamin D and IL-10 deficiency in preterm neonates with bronchopulmonary dysplasia. Front Pediatr.2018;6:24-6.
46. Cetinkaya M, Cekmez F, Erener-Ercan T, Buyukkale G, DemirhanA,Aydemir G.Maternal/neonatal vitamin D

deficiency: a risk factor for bronchopulmonary dysplasia in preterm J Perinatol. 2015; 35:813–7

47. Gäddnäs FP, Sutinen MM, Koskela M, Tervahartiala T, Sorsa T, Salo TA.Matrix-metalloproteinase-2, -8 and -9 in serum and skin blister fluid in patients with severe sepsis. Crit Care. 2020; 14:1- 49

48. Jones T, Reilly J, Anderson B, Miano T, Dunn T, Weisman A. Elevated plasma levels of matrix metalloproteinase-3 and tissue inhibitor of matrix. Swiss Med Wkly. 2010; 28(150):20-32

Citation: Noura M.Ibrahim Elbakry; Ayat Mostafa Mohamed; Ahmed N. Gamil. "Role of Vitamin D and Parathyroid Hormone Levels in Prediction of Late Onset Sepsis among Preterm Infants: A Prospective Cohort study". *Annals of Neonatology*, 2024; 6(2): 60-79. doi: 10.21608/anj.2024.276513.1087