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**Original Research Article**

# Association between vitamin D levels and early onset sepsis in infants: a prospective observational study

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## ABSTRACT

**Background:** An appropriate vitamin D supplementation that leads to higher maternal 25-OHD levels during pregnancy which would subsequently have beneficial effects in prevention of both maternal and neonatal morbidities. Aim of the study was to evaluate the effect of vitamin D levels on early-onset sepsis (EOS) in term infants admitted in Neonatal Intensive Care Unit of Lotus children's hospital, Hyderabad.
**Methods:** This prospective observational study was conducted in NICU of Lotus Children's Hospital, Hyderabad from January 2016 to May 2016. Thirty nine term infants with clinical and laboratory findings of EOS (study group) and thirty nine healthy infants with no signs of clinical/laboratory infection (control group) admitted to LCH-NICU who fulfilled the eligibility criteria were enrolled in this study. Blood was drawn at the time of admission during the first 3 postnatal days of life in both groups for measurement of 25-hydroxyvitamin D (25-OHD) levels.
**Results:** Out of total of 78 infants (48.7%) was male and (51.3%) was female. CRP level was more than 20 in 64%, 11 to 20 in 28% and 0 to 10 in 8% of study population, while blood culture was positive in 44% of the study group. No significant difference was found between two groups in terms of sex, birth weight, gestational age, mode of delivery, sun protection. 25-OHD levels in the study group were significantly lower compared with those in the control group ($P<0.05$). The majority (64.1%) of infants in the sepsis group had a mean 25-OHD level >12 ng $ml^{-1}$, which was statistically significant ($P<0.05$).
**Conclusions:** This study reports significantly lower neonatal 25-OHD levels in term infants with EOS compared with those who did not have sepsis.

**Keywords:** Infant, Study, Vitamin D

## INTRODUCTION

NS is defined as a clinical syndrome characterized by signs and symptoms of infection with or without accompanying bacteremia in the first month of life. It encompasses various systemic infections of the newborn such as septicaemia, meningitis, pneumonia, arthritis, osteomyelitis etc., but it does not include superficial infections like thrush.[1] Vitamin D may enhance the innate immune response by induction of cathelicidin (LL-37), an endogenous antimicrobial peptide produced by macrophages and neutrophils. Thus, the relationship between vitamin D status and LL-37 production may be of importance for host immunity.[2]

Current vitamin D intake recommendations during pregnancy range from 400 to 600 IU per day to 1500 to 2000 IU per day according to the Institute of Medicine report and Endocrine Society report, respectively.[3-5] Recently, two new randomized controlled studies showed that a daily intake of higher (4000 IU per day) vitamin D resulted with higher circulating 25-OHD levels in

pregnant women compared with low doses (200 IU per day and 2000 IU per day).[6,7]

Therefore, it was suggested that higher vitamin D supplementation might be required for prevention of hypovitaminosis D and achievement of normal circulating 25-OHD levels (40 to 60 ng $ml^{-1}$) during pregnancy, which would also decrease the incidence of co-morbidities of pregnancy.[8,9]

A more recent study showed that lower maternal 25-OHD levels were associated with increased risk of dental caries in infants.[10] All these data suggest the role of appropriate vitamin D supplementation that leads to higher maternal 25-OHD levels during pregnancy which would subsequently have beneficial effects in prevention of both maternal and neonatal morbidities.

Hence present study was planned to evaluate the effect of vitamin D levels on early-onset sepsis (EOS) in term infants admitted in Neonatal Intensive Care Unit of Lotus children's hospital, Hyderabad.

## METHODS

### *Place of study*

This study is prospective observational study conducted in NICU of Lotus Children's Hospital, Hyderabad. A study was conducted from January 2016 to May 2016.

***Sample size:*** 78

### *Inclusion criteria*

*Study group:* Infants with clinical and laboratory findings of EOS admitted to LCH NICU within 72 hours of life.

*Control group:* Healthy infants with no signs of clinical/laboratory infection admitted to LCH NICU within 72 hours of life.

### *Exclusion criteria*

- Presence of maternal risk factors,
- Refusal of parental consent,
- Major congenital abnormalities

Thirty nine term infants with clinical and laboratory findings of EOS (study group) and thirty nine healthy infants with no signs of clinical/laboratory infection (control group) admitted to LCH-NICU who fulfilled the eligibility criteria were enrolled in this study.

### *Consent*

An informed consent was obtained from the parents/guardians prior to enrolment. All data was recorded in predesigned structured proforma. The study was approved by institutional Ethics Committee.

### *Sample collection*

Blood was drawn at the time of admission during the first 3 postnatal days of life in both groups for measurement of 25-hydroxyvitamin D (25-OHD) levels.

### *Sepsis related clinical signs*

Temperature instability, apnea, need for supplemental oxygen, need for ventilation, tachycardia or bradycardia, hypotension, feed intolerance, abdominal distension.

### *Statistical analysis*

Data were statistically described in terms of mean (±SD), frequencies (number of cases) and percentages when appropriate.

## RESULTS

The study population included a total of 78 infants. From these infants, 39 had suspected neonatal sepsis (study group) and 39 did not have any findings of sepsis (control group). Mean birth weight of the control group was 2410±590 gm. Mean birth weight of the case group was 2140±660 gm.

**Table 1: Sex wise distribution of study subjects.**

| | Group | | Total |
|---|---|---|---|
| Sex | Controls | Cases | |
| Female | 19 (48.7%) | 21 (53.8%) | 40 (51.3%) |
| Male | 20 (51.3%) | 18 (46.2%) | 38 (48.7%) |
| **Total** | **39** | **39** | **78** |

p- Value - 0.82

A total of 78 infants (48.7%) were male and (51.3%) were female. The pre-term and term babies were distributed equally among cases and controls.

**Table 2: Distribution of study subjects as per the gestational age.**

| | Group | | Total |
|---|---|---|---|
| Gestational age | Controls | Cases | |
| Pre-term | 17 (43.6%) | 22 (56.4%) | 39 (50%) |
| Term | 22 (56.4%) | 17 (43.6%) | 39 (50%) |
| **Total** | **39** | **39** | **78** |

p- Value - 0.36

**Table 3: Distribution of study subjects as per the sun protection offered.**

| | Group | | Total |
|---|---|---|---|
| Sun protection | Controls | Cases | |
| No | 36 (92.3%) | 35 (89.7%) | 71 (91%) |
| Yes | 3 (7.7%) | 4 (10.3%) | 7 (09%) |
| **Total** | **39** | **39** | **78** |

p- Value - 1.0

In 91% of babies no sun protection was offered to them.

**Table 4: Distribution of study subjects as per the mode of delivery.**

| | Group | | Total |
|---|---|---|---|
| Delivery | Negative | Positive | |
| LSCS | 25 (64.1%) | 31 (79.5%) | 56 (71.8%) |
| Vaginal | 14 (35.9%) | 8 (20.5%) | 22 (28.2%) |
| **Total** | **39** | **39** | **78** |

p- Value - 0.21

71.8 % of the study population was born via cesarean section and 28.2% were born via vaginal delivery.

**Table 5: Distribution of cases as per the culture result.**

| Culture (Cases) | N | % |
|---|---|---|
| Negative | 22 | 56% |
| Positive | 17 | 44% |
| **Total** | **39** | **100%** |

56% of the cases were culture negative and 44% were culture positive.

**Table 6: Distribution of cases as per C reactive protein levels.**

| CRP (Cases) | N | % |
|---|---|---|
| 0 to 10 | 3 | 8% |
| 11 to 20 | 11 | 28% |
| >20 | 25 | 64% |
| **Total** | **39** | **100%** |

64% of cases were showing CRP levels of more than 20.

**Table 7: Study of variables in cases and controls.**

| Variables | Group | Mean | SD | SEM | p-value |
|---|---|---|---|---|---|
| Birth Weight (Kg) | Controls | 2.41 | 0.59 | 0.09 | 0.06 |
| | Cases | 2.14 | 0.66 | 0.11 | |
| Maternal Age (years) | Controls | 25.44 | 5.01 | 0.80 | 0.117 |
| | Cases | 27.03 | 3.75 | 0.60 | |
| WBC (in thousand) | Controls | 12.33 | 2.81 | 0.45 | 0.928 |
| | Cases | 12.40 | 3.98 | 0.64 | |
| Platelets (in lakhs) | Controls | 3.08 | 1.47 | 0.24 | 0.065 |
| | Cases | 2.54 | 1.02 | 0.16 | |

No significant difference was observed among cases and controls in terms of WBC count, platelet count sex, birth weight, gestational age, mode of delivery, sun protection. Similarly, no significant difference was detected with respect to maternal demographic features including maternal age between the two groups. 25-OHD levels in the study group were significantly lower compared with those in the control group (P<0.05).

**Table 8: Comparison of vitamin D levels among cases and controls.**

| Group | Mean Vit. D levels | SD | SEM | p- value |
|---|---|---|---|---|
| Controls | 26.46 | 22.01 | 3.52 | < 0.01 |
| Cases | 14.69 | 4.45 | 0.71 | |

**Table 9: Association of vitamin D levels with early onset sepsis.**

| Vitamin D levels | Group | | Total |
|---|---|---|---|
| Vitamin D levels | Controls | Cases | |
| </= 12 | 5 (12.8%) | 14 (35.9%) | 19 (24.4%) |
| > 12 | 34 (87.2%) | 25 (64.1%) | 59 (75.6%) |
| **Total** | **39** | **39** | **78** |

p- Value < 0.05

The majority (64.1%) of infants in the sepsis group had a mean 25-OHD level >12 ng $ml^{-1}$, which was statistically significant (P<0.05).

## DISCUSSION

This study showed that neonatal 25-OHD levels were significantly lower in infants with early onset sepsis (EOS) who were admitted.

In the study by Manroe BL et al both 25 (OH)-D and 1,25 (OH)-D levels were lower among non-survivors in critically ill patients.[11] Matthews et al noted in their surgical ICU cohort that most deaths occurred at vitamin D levels less than 32 nmol/L and that no deaths occurred at levels higher than 65 nmol/L.[12] Lawn JE et al reported a reversed J-shape relation between 25 (OH)-D and all-cause mortality, suggesting that too much and too little are deleterious. A serum 25 (OH)-D of 50 to 60 nmol/L was associated with the lowest mortality risk.[3]

The results of this meta-analysis suggest that vitamin D levels below 50 nmol/L, increase 30-day mortality and in-hospital mortality with 76% and 79% respectively. To date, only four randomized trials in adult critically ill patients have been published, which were designed to study normalisation of vitamin D levels and its possible adverse effects such as hyper-calcemia and hyper-calciuria.[13,14] These studies were not sufficiently powered to investigate the effects of vitamin D normalization and potential benefits on hard outcomes such as incidence of severe infections and/or ICU mortality. The recently published Lancet review supports the relation between 25 (OH)-D deficiency and all-cause mortality in observational studies.

## CONCLUSION

In conclusion, this study reports significantly lower neonatal 25-OHD levels in term infants with EOS compared with those who did not have sepsis. For elucidation of the exact mechanism and preventive role of vitamin D on EOS, future experimental and clinical studies are warranted.

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