



# The Relation Between Maternal / Neonatal Vitamin D Levels and Early Onset Neonatal Sepsis

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**Abstract:** In addition to its classical role in bone metabolism, vitamin D also has an immunomodulatory effects on immune function. Our aim was to determine the relation between serum 25-hydroxy vitamin D(25(OH)D) concentrations in newborns and their mothers with early onset neonatal sepsis (EOS). Also we aim to study the effect of severity of vitamin D deficiency on incidence of EOS. The design comprises a hospital- based case- control study. The study group consisted of 50 newborns with EOS who was admitted to neonatal intensive care unit and their mothers. Controls were 50 healthy newborns of the same age as the study group and their mothers. The study subjects were divided into insufficient, moderate and severe deficiency according to vitamin D level. There is no significant statistical difference between study and control groups in gestational week, birth weight, birth height, head circumference and age. The mean serum 25(OH)D concentrations in the study group newborns were significantly lower than those of the control group (11.58±4.883 ng/ml and 28.78±6.453 ng/ml respectively). The 25(OH)D concentrations of newborns were highly correlated with mothers' serum in both groups. Severe vitamin D deficiency was significantly more common in the sepsis group. Data shows that 25(OH)D concentrations of the newborns were highly correlated with the level of CRP, duration of hospital stay, and complications caused by sepsis. Our findings suggest that newborns with vitamin D deficiency may have an increased risk of suffering from EOS. Newborns with more vitamin D deficiency were found to have higher CRP levels, a longer hospital stay, and a higher incidence of complications. The strong positive correlation between newborns' and their mothers' 25(OH)D concentrations makes that adequate vitamin D supplementation of mothers during pregnancy is of great importance, through a proper ante-natal care, especially in winter months.

**Keywords:** Neonatal, Vitamin D, Early Onset Sepsis

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## 1. Introduction

Vitamin D deficiency is a worldwide complication with prevalence ranging from 18-84% that is more dependent upon geographic region, ethnicity, type of clothing and dietary intake. The main role of vitamin D in the body is to make sure there is enough calcium and phosphate to keep the bones healthy and strong [1]. In addition to this classical role in bone metabolism, vitamin D also has immunomodulatory effects on immune function [3].

Vitamin D has also been found to have some neonatal protective properties against infectious diseases by regulating

of the innate-adaptive immune system, anti-inflammatory effects, increased monocyte responses, and enhanced mucosal barrier as well as by endothelial function [15-26]. There is close and deep relationship between maternal and fetal vitamin D [29].

Maternal vitamin D status in pregnancy affects the status of the infant for the first few months of life. If maternal vitamin D status is good during the last stages of pregnancy the newborn child should have adequate vitamin D status for sometime after birth in the absence of significant input from diet [4].

Early onset neonatal sepsis is a clinical syndrome characterized by sign and symptoms of infection with or

without bacteremia in the first 5-7 days of life which is still an important cause of morbidity and mortality among infants [23].

Although some studies reported a link between vitamin D deficiency and critical illness in adults, a direct relationship has not been directly shown yet. However, few studies evaluated the association between early onset sepsis (EOS) and maternal/neonatal vitamin D levels.

The objective of this prospective study is to determine the possible role of maternal and neonatal plasma vitamin D levels on EOS development in term infants. We also aim to study the effect of severity of vitamin D deficiency on incidence of EOS.

## 2. Study Design

This is a prospective case-control study that included 50 term infants, who will be admitted to neonatal care unit in Children's Hospital, Cairo University, Egypt with clinical and laboratory findings of early onset sepsis, from January 2013 to May 2014.

Sepsis Criteria defined by Gitto et al [8]

Highly probable sepsis at least three sepsis-related clinical signs, CRP > 1 mgdl-1, with two or more other related serum parameters in addition to CRP, Blood culture positive or negative. Probable Sepsis less than 3 sepsis related signs, CRP > 1 mgdl-1, at least two other altered serum parameters in addition CRP. Possible Sepsis less than 3 sepsis related clinical sign, CRP < 1mgdl-1, Less than 2 other altered serum parameter, Blood culture negative.

Clinical signs of sepsis: respiratory (distress, apnea, tackypnea, or hypoxia), cardiological (tachycardia or bradycardia), hemodynamics (bad color, por peripheral hypoperfusion, hypotension), neurological (irritability, lethargy, hypotonia, hypo activity, seizures), gastrointestinal (poor feeding, abdominal distension, feeding intolerance), temperature (fever > 38 c, hypothermia < 36 c), metabolic (acidosis or hyperglycemia).

The study group will consist of 50 term neonates who are clinically suspected to have an early infection from the first day of life. Blood for neonatal and maternal vitamin D levels will be obtained from all infants and their mothers at the time of hospital admissions. Only infants with high probable sepsis will consist the study group. For this group at time of admission CBC differential, CRP, and blood culture will be done, and it will be repeated after 48 hours. Complications caused by sepsis (respiratory distress, tachycardia, dehydration, meningitis, ets.....), and duration of hospital stay will be also recorded.

Fifty healthy neonates, with no prenatal risk factor for early onset sepsis were enrolled in the study as a Control group.

In both groups, maternal samples will be obtained at the postpartum period at the time of neonates' hospitalization. Newborn's gestational ages, birth weight, birth height, and birth head circumference were elicited from health records brought by parents. Also recorded was whether the newborns

were breastfeeding or not.

The severity of vitamin D deficiency will be related to neonatal sepsis. Neonates will be divided into three groups in terms of insufficient, moderate and severe vitamin D deficiency according to maternal and neonatal vitamin D levels and a possible association between vitamin D deficiencies and clinical/laboratory proven sepsis will be investigated.

Both genders are included in the study, age up to 72 hours.

Venous blood specimens were collected from all neonates included in the study, and their mothers. The serum samples were stored at -20 c and protected from direct exposure to sunlight until the analysis. For the quantitative determination of 25(OH) D concentrations in the serum samples, a commercially available 25-hydroxy vitamin D3 RIA (specific radioimmunoassay) kit (BIOSOURCE Catalog No. KIP1961, Nivelles, Belgium) was used according.

For levels of vitamin D less than 40 ng/ml is considered insufficiency, while levels less than 20 ng/ml is considered deficiency according to institute of medicine (IOM) report and the consensus report on nutritional rickets [22, 24, 25].

Insufficient: 20-40 ng/ml

Moderate deficiency: 10-20 ng/ml

Severe deficiency: < 10 ng/ml

Infants were treated with appropriate antibiotic therapies including ampicillin in combination with gentamicin for the first-line therapy of EOS used in the hospitals of Egypt. Neonates with positive cultures were treated with antibiotics according to the causative organisms detected by the culture. The antimicrobial therapy was stopped after clinical and laboratory improvement.

The study was approved by the local research ethics committee of Cairo university Hospital for children and written informed consents were obtained from the parents of all neonates to share in the study.

## 3. Statistical Analysis

Data were statistically described in terms of mean  $\pm$  standard deviation ( $\pm$  SD), median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student t test for independent samples in comparing 2 groups when normally distributed and Mann Whitney U test for independent samples when not normally distributed. Comparison of Numerical variables between more than two groups was done using Kruskal Wallis test with Mann Whitney test as a posthoc multiple 2-group comparison. For comparing categorical data, Chi square ( $\chi^2$ ) test was performed. Exact test was used instead when the expected frequency is less than 5. Correlation between various variables was done using Pearson moment correlation equation for linear relation in normally distributed variables and Spearman rank correlation equation for non-normal variables and or non-linear monotonic relations. p values less than 0.05 was considered statistically significant. All statistical calculations were done using computer

program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) release 15 for Microsoft Windows (2006).

## 4. Results

In this study, 50 (27 males, 23 females) cases and 50 controls (26 males, 24 females) were involved. There was no significant difference in postnatal mean age between case and control groups (10.9±9.2 day and 9.6±7.06 day, respectively,

$p=0.234$ ). The anthropometric characteristics of newborns are shown in Table 1. As the table shows, there is no significant statistical difference between study and control groups in gestational week, birth weight, birth height, and head circumference. All cases were exclusively breast-fed. The number of mothers in the study group who never used vitamin D supplementation (23 mothers, 46% of the study group) was significantly higher than that in the control group (8 mothers, 16% of the control group) ( $p<0.05$ ).

**Table 1.** Birth anthropometric measures and gestational age of new-borns.

Birth mean (s. d.)	Study group	Control group	p-value
Weight (g)	3150.0 (569.66)	3135.0 (422.7)	0.900
Length (cm)	49.15 (2.99)	49.79 (1.31)	0.408
Head circumference (cm)	34.16 (1.78)	34.71 (1.16)	0.317
Gestational age (week)	39.17 (1.68)	39.23 (0.78)	0.659

$P>0.05$  no significant difference observed.

The mean serum 25(OH)D concentrations in the study group newborns were lower than those of the control group (11.58±4.883 ng/ml and 28.78±6.453 ng/ml respectively) with a high statistical significant value  $p=0.000$ . The majority (81%) of infants in the sepsis group had a mean 25-OHD < 11 ng/ml. Also mean serum 25(OH) D concentrations in the mothers of the study group were lower than in the mothers of the control group (21.98±8.925 and 44.78±7.407 respectively) with a high statistical significant value  $p=0.000$ .

The 25(OH)D concentrations of newborns were highly correlated with mothers' serum levels ( $r=0.79$ ,  $p<0.05$ ) in the study group. The correlation between 25(OH)D concentrations in newborns and their mothers in control

group is also considerable ( $r=0.53$ ;  $p<0.05$ ).

It was noticed that both maternal and neonatal 25-OHD levels were significantly higher in the summer months and with regular exposure to sunlight (mean 24.3±21 ng/dl compared to 13.6±10.8 in winter months)  $p<0.05$ .

The data showed that, 46 patients (46%) had severe vitamin D deficiency (<10 ng/dl), while 8 patients (8%) had moderate deficiency (10-20 ng/dl), and 21 patients (21%) showed vitamin D insufficiency (20-40 ng/dl), while 25 patients (25%) have normal level of vitamin D all in the control group. Table 2 shows detailed information about the distribution of vitamin D level among the newborns of the two groups and their mothers.

**Table 2.** Serum 25 (OH)D distribution of newborns and their mothers.

25 (OH)D (ng/ml)	Study group, N=50 (%)	Control group, N=50 (%)	Total N=100 (%)
<b>Newborns</b>			
Severe deficiency	40 (80.0)	6 (12.0)	46 (46.0)
Moderate deficiency	6 (12.0)	2 (4.0)	8 (8.0)
Insufficiency	4 (8.0)	17 (34)	21 (21.0)
Normal	0 (0.0)	25 (50.0)	25 (25.0)
<b>Mothers</b>			
Severe deficiency	32 (64.0)	7 (14.0)	39 (39.0)
Moderate deficiency	10 (20.0)	4 (8.0)	14 (14.0)
Insufficiency	8 (16.0)	29 (58.0)	37 (37.0)
Normal	0 (0.0)	10 (20.0)	10 (10.0)

Table 3 shows the relation between CRP level, duration of hospital stay, complications caused by sepsis, and severity of vitamin D deficiency.

Data shows that 25(OH)D concentrations of newborns and

their mothers were highly correlated with the level of CRP, duration of hospital stay, and complications caused by sepsis ( $r=0.425$ ,  $r=0.512$ ,  $r=0.524$  respectively)  $p$  for all  $<0.05$ .

**Table 3.** The relation between CRP levels, hospital stay, complications and severity of vitamin D deficiency.

	CRP1 (mean±st)	CRP2 (mean±st)	Hospital stay (mean±st)	ComplicationsNo. of cases (%)
Severe deficiency	19.00±10.296	53.75±18.301	15.00±8.246	29 (58)
Moderate deficiency	11.54±3.799	51.00±17.263	11.85±5.610	13 (26)
Insufficiency	5.75±1.708	23.75±7.089	6.40±2.160	8 (16)

Cases with cultural proven sepsis were much higher in the study group than those in the control group (16 cases in the study group, compared to 5 cases in the control group), with the predominance of E. coli in positive cases. ( $p=0.009$ ).

## 5. Discussion

The main aim of our study is to detect the levels of vitamin

D in both groups, and determine its relation to the development of neonatal sepsis. We find that serum 25(OH)D concentrations in newborns with neonatal sepsis (study group) were lower than those of the healthy newborns (control group) and most newborns who have the serum 25(OH)D <11 ng/ml were more likely to develop sepsis. The study also showed that the mean 25(OH)D concentrations in mothers of the study group were lower than those of the control group. Levels of 25-OHD were also higher in summer and with regular vitamin D supplementation. Furthermore, it was found that 25(OH)D concentrations of newborns are highly correlated with 25(OH)D concentrations of their mothers in both the study and control groups. It was found also that degree of severity of vitamin D deficiency is highly correlated with level of CRP, duration of hospital stay, and complications caused by sepsis.

These results were in agreement with the study done by Cetinkaya [5], who stated that maternal and neonatal 25-OHD levels were significantly lower in term infants who were admitted with EOS. Neonatal 25-OHD levels were positively correlated with maternal 25-OHD levels.

Also these results were in agreement with the result of the study done by Karatekin [16], who was studying the effect of vitamin D deficiency on the development of lower respiratory infections.

These findings are important because they show that newborns with vitamin D deficiency may have an increased risk of suffering from EOS, and the EOS is common cause of morbidity and mortality in newborn period, especially in developing countries [30].

Valdivielso [28] provided one of the earliest studies that suggested that vitamin D could up regulate the production of anti-microbial peptides. They demonstrated that 1,25(OH)2D3 treatment up-regulated cathelicidin mRNA in several cell lines and primary cultures including keratinocytes, neutrophils, and macrophages.

Baek [2] stated that, vitamin D has a physiological role beyond its well-known role in skeletal homeostasis. Vitamin D as an immunomodulatory targeting various immune cells, including monocytes, macrophages, dendritic cells (DCs), as well as T-lymphocytes and B-lymphocytes, hence modulating both innate and adaptive immune responses. Besides being targets, immune cells express vitamin D-activating enzymes, allowing local conversion of inactive vitamin D into 1,25(OH)2D3 within the immune system.

In addition to systemic inflammatory response modulation, vitamin D also has effects on the local control of pathogens. Vitamin D was reported to inhibit the growth of and/or killed strains of *Staphylococcus aureus*, *S. pyogenes*, *k. pneumoniae*, and *E. coli*. Many examples document the benefits of having an optimal vitamin D level in gram negative bacteria. Treatment with 25(OH)D protected 3A cells of the placenta against cell death after infection with *E. coli* [20].

In recent years, vitamin D was reported to have a complex effect on immune functions as it enhanced innate immunity while it also downregulated the acquired immune responses [7, 18]. The mechanical barrier of the skin and other

epithelial surfaces constitute the first barrier to infections and activated 25-OH vitamin D has an important role in maintaining the integrity of epithelial cells by encoding the proteins needed for several tight junctions [31].

Vitamin D induce down regulation of the cytokine response. Th1 cytokine profile is vital for clearance of certain organisms and ancillary immune activity, and a limiting effect on this cytokine profile may result in reduced chances for overcoming infections. This fact can explain why patients with vitamin D deficiency have longer stay in the hospital, higher CRP levels, and more incidences of complications due to spreading of infections [12].

This indicates the economic burden due to vitamin D deficiency in newborns on family and community. This economic burden is a short term one. Considering that vitamin D deficiency can lead to chronic diseases in long term, the economic burden of vitamin D deficiency in long term would be much more. Hence, the main implication of the study is that decreasing the vitamin D deficiency in newborns may reduce their morbidity risk. Studies are needed in this direction as well.

A study done by Moller, et al [23] investigated the prevalence of vitamin D deficiency in critically ill children admitted to the pediatric intensive care unit, a high rate of vitamin D deficiency was present among critically ill children and was associated with greater severity of critical illness. However, to the best of our knowledge, there are few studies investigated the association between neonatal sepsis and maternal/neonatal 25-OHD levels in both term and preterm infants in North Africa.

Similar to other investigations done by [4, 19, 5], our study showed that the blood 25(OH)D concentrations in the neonates correlated well with the maternal 25(OH)D concentrations. Yang et al. demonstrated that mothers and their neonates with early onset sepsis had lower 25-OHD levels in comparison with their counter-parts in the control group, leading to the neonatal early-onset sepsis risk for full-term infants [34]. Karras et al. stated that maternal vitamin D level has been found to be potentially linked to a decrease risk of neonatal infectious diseases including respiratory infections and sepsis [17]. This important correlation between the concentration of 25(OH)D in the mothers and their newborns, make regular intake of vitamin D during pregnancy, is of utmost importance. This can be achieved through careful antenatal care and proper educational programs for the mothers about the role of vitamin D in the development of immunity of their kids.

## 6. Conclusion

Our study concluded that lower vitamin D levels is associated with higher incidence of neonatal sepsis. Neonates with lower vitamin D levels have recorded longer stay in the hospital, with more incidences of complications and higher CRP levels. Vitamin D concentrations in the neonate were well correlated with their mothers.

## Authors Contributions

DK, I SH, conceived the study, interpreted the data, and critically revised the reports and obtained clinical information from study participants. All authors read and approved the final manuscript.

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## Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

## Conflict of Interest

The authors declare no conflict of interest.

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No.

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