

LOWER MATERNAL VITAMIN-D LEVELS' ASSOCIATION WITH EARLY-ONSET NEONATAL SEPSIS IN TERM NEONATES

Muhammad Tariq Nadeem, Fahim Akhtar, Mubashra Samina

Combined Military Hospital Malir Pakistan

ABSTRACT

Objective: To determine the association of low maternal serum vitamin-D levels with serum vitamin-D levels of their term neonates and higher risk of early onset neonatal sepsis (EOS).

Study Design: Prospective observational study.

Place and Duration of Study: Neonatal intensive care unit (NICU) of Department of Pediatrics; Combined Military Hospital (CMH) Malir Cantt Karachi, from Apr 2016 to Apr 2017.

Material and Methods: Ninety three term neonates with EOS formed the "sepsis group" and equal number (93) of healthy term neonates without sepsis were included in the control group selected as per inclusion criteria. Blood samples of mothers and their neonates were drawn during the first 72 hours after delivery for measurement of serum vitamin-D levels.

Results: Mean serum vitamin-D levels were 18.16 ± 8.21 ng/ml and 13.93 ± 13.29 ng/ml in the mothers and their neonates respectively in the sepsis group and were significantly lower (p -value <0.001) than the mean serum vitamin-D levels of 33.35 ± 12.70 ng/ml and 27.92 ± 7.58 ng/ml in the mothers and their neonates respectively in the control group. Vitamin-D deficiency was found in significantly higher number of cases in mothers (88.17%) and neonates (82.80%) in sepsis group as compared to 52.69% mothers and 39.78% neonates in control group (p -value <0.001). There were 14 (15.05%) cases of culture proven sepsis in the study group as compared to just 01 (1.08%) case of culture proven sepsis in control group which was statistically significant (p -value <0.001).

Conclusion: Lower maternal serum vitamin-D levels are associated with lower serum vitamin-D levels and higher risk of EOS in their term neonates.

Keywords: Early-onset neonatal sepsis, Maternal vitamin-D level, Neonatal vitamin-D level, Vitamin-D deficiency.

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INTRODUCTION

Neonatal sepsis is a clinical syndrome of systemic infection occurring in neonates (birth to 28 days of life). Early-onset neonatal sepsis (EOS) has been variably defined as the onset of sepsis within 72 hours or within 5 days after birth but mostly presents within 72 hours. Late-onset sepsis (LOS) occurs after this period. EOS is caused by pathogens transmitted vertically from mother to neonate before or during delivery¹.

The neonatal sepsis is usually a fulminant disease and can result in death or significant long term disabilities. It is the third leading

cause of neonatal mortality after prematurity and intra-partum complications like birth asphyxia. It is responsible for 1.5 to 2.0 million deaths per year and accounts for more than 25% of neonatal deaths worldwide². Pakistan has one of the highest neonatal mortality rate (46/1000 live births) and ranks third in the world with a share of 7% neonatal deaths³.

High prevalence and morbidity of neonatal sepsis has led to the efforts for its prevention by identifying predisposing risk factors and early management. Risk factors for EOS include both maternal and neonatal factors. Prolonged labor, chorioamnionitis, maternal intrapartum fever, prematurity, prolonged rupture of membranes, galactosemia and instrument assisted delivery are important risk factors⁴.

Correspondence: Dr Muhammad Tariq Nadeem, Consultant Pediatrician, CMH Lahore Pakistan

Email: nadeemchauhan31@gmail.com

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Lower maternal and neonatal vitamin-D levels are also being implicated as a risk factor for EOS because of its immune modulatory effects⁵.

25-hydroxyvitamin D (25-OHD) or cholecalciferol is a fat soluble, pleiotropic vitamin. It modulates numerous skeletal and extra-skeletal functions. Adequate vitamin-D status during pregnancy has important beneficial outcomes both for mother and neonate which include reduction in risks of eclampsia, cesarean and preterm delivery⁶, neonatal hypocalcemia, transient tachypnea of newborn, respiratory distress syndrome, bronchopulmonary dysplasia and intra-uterine growth retardation⁷.

Vitamin-D receptors are expressed on immune cells that greatly influences immunity and susceptibility to microbial infections. The vit-D enhances immunity by inducing the production of human cathelicidin (LL-37) which has antimicrobial and anti-endotoxin activity⁸. Neonates have immature innate and adaptive immunity and low vitamin-D levels can make them even more vulnerable to infections and sepsis. Vitamin-D deficiency is prevalent in Pakistani mothers and their newborns⁹. Recently, low levels of circulating 25-OHD have been shown to be strongly associated with infectious diseases and sepsis in adults¹⁰. Some international studies have reported the association of lower maternal vitamin-D levels with increased risk of EOS^{11,12}. However, very few studies have been done in Pakistan to evaluate this association.

Therefore, the aim of this study is to determine the association of low maternal serum vitamin-D levels with serum vitamin-D levels of their term neonates and higher risk of early EOS. If we are successful in establishing such an association, it may well help to substantially decrease the morbidity and mortality associated with neonatal sepsis by preventing the vitamin-D deficiency in expectant mothers.

PATIENTS AND METHODS

It was prospective observational study conducted in Neonatal Intensive Care Unit

(NICU) of department of Pediatrics, Combined Military Hospital (CMH) Malir Cantt Karachi, from Apr 2016 to Apr 2017. The study was approved by Institutional Ethics Committee.

The study population was divided into two groups; sepsis group and control group comprising of 93 neonates each enrolled according to the following inclusion criteria;

Neonates born at term (gestational age ≥ 37 weeks to 42 weeks at birth) presenting within 72 hours of birth with sepsis - related clinical features along with at least one supportive laboratory evidence including raised C-reactive protein (CRP) or Blood culture positivity or altered blood cell counts (abnormal white blood cells count or raised I: T ratio or thrombocytopenia) as mentioned in table-I were included in sepsis group. Healthy term neonates with same postnatal age admitted for routine observation were included in the control group. Neonates with following criteria were excluded from study;

- Preterm and post term neonates (less than 37 and more than 42 weeks of gestation respectively)
- Meconium aspiration
- Perinatal asphyxia
- Babies who underwent cardiopulmonary resuscitation
- Major congenital abnormalities
- Refusal of parental consent

An informed consent was obtained from the parents prior to enrolment. Neonates who presented with onset of sepsis within 72 hours of birth were admitted in NICU. Healthy term neonates of control group were kept in 'mother based care' or NICU for work up. Blood samples of mothers and their neonates were drawn at the time of admission during the first 72 hours of life in both groups for measurement of vitamin-D levels by "chemiluminescence immunoassays" method. Serum vitamin-D level: $< 30\text{ng/ml}$ was defined as vitamin-D deficiency⁶.

C-reactive protein (CRP) level: ≥ 6 ng/ml was defined as "raised or positive"¹³.

Blood samples were obtained by peripheral venipuncture under complete aseptic conditions. Sepsis work-up included complete blood

age, birth weight, gender and mode of delivery of all neonates were also recorded.

Data were compiled and statistically analyzed by using SPSS-21 and MS Excel 2016 software. Percentages, means and standard

Table-I: Modified Clinical and laboratory criteria for diagnosis of neonatal sepsis as defined by the European Medicine Agency (EMA)¹.

Clinical Features	Investigations
<ul style="list-style-type: none"> ➤ General features: <ul style="list-style-type: none"> • Fever • Hypothermia • Lethargy • Irritability ➤ Cardiovascular instability: <ul style="list-style-type: none"> • Bradycardia • Tachycardia • Rhythm instability • Reduced urinary output < 1 ml/kg/h • Hypotension • Mottled skin • Impaired peripheral perfusion ➤ Respiratory instability: <ul style="list-style-type: none"> • Apnea • Tachypnea • Supplemental oxygen requirements or • Requirement for ventilatory support ➤ Gastrointestinal: <ul style="list-style-type: none"> • Feeding intolerance • Poor sucking • Abdominal distension • Necrotizing enterocolitis ➤ Neurological: <ul style="list-style-type: none"> • Sunken, bulging or pulsating fontanel • Seizures, tremors or jitteriness • High pitched cry • Hypotonia ➤ Skin and subcutaneous lesions: <ul style="list-style-type: none"> • Petechial rash • Sclerema 	<ul style="list-style-type: none"> ➤ WBCs: <ul style="list-style-type: none"> • $< 5 \times 10^9$/L or • $> 30 \times 10^9$/L • Immature to total neutrophil ratio (I/T): > 0.2 ➤ Platelet count: $< 100 \times 10^9$ /L ➤ CRP: ≥ 06 ng/ml ➤ Hyperglycemia (blood glucose > 180 mg/dL) or ➤ Hypoglycemia (blood glucose < 45 mg/dL) ➤ Metabolic acidosis: <ul style="list-style-type: none"> • Serum lactate: > 2.2 mm/L ➤ Blood culture (early growth) ➤ Cerebrospinal fluid examination & culture (in suspected cases of CNS infections). ➤ Chest X-ray having evidence of chest infection ➤ Radiological evidence of NEC

counts, total leukocyte count, immature to total neutrophils (I:T) ratio or band cell count, CRP level and blood culture. All the peripheral blood smears were analyzed by pathologists. The maternal demographic features including age, rural/urban origin, parity, residing in flats or open houses, wearing of burqa or hijab (sun protective clothing) were recorded. Gestational

deviations were calculated by descriptive analytic tests. The *p*-values of different parameters were calculated by using Pearson's chi-square test and t-test. A *p*-value < 0.05 was considered statistically significant.

RESULTS

Ninety three babies presented with onset of sepsis within 72 hours of birth during the

study period and were included in the sepsis group. The diagnosis of sepsis was made as per EMA criteria (table-I). An equal number of healthy neonates (n=93) were included in the control group.

There was statistically no significant difference between the two groups in terms of maternal and neonatal demographic features (table-II).

Statistically, significantly higher number of cases were CRP positive in the sepsis group as compared to the control group (p -value<0.001).

compared to the mothers and their neonates in the control group (table-V). Neonatal vitamin-D levels were associated with maternal vitamin-D levels and majority of the neonates born to vitamin-D deficient mothers were also vitamin-D deficient (table-V).

There were 14 (15.05%) cases of culture proven EOS in the study group as compared to just 01 (1.08%) case of culture proven EOS in the control group (table-V) which was statistically significant (p -value<0.001). Gram negative organisms were the predominant

Table-II: Neonatal & maternal demographic variables.

Demographic variables	Sepsis group=93 n (%)	Control group=93 n (%)
Neonatal		
Male	40 (43.01)	46 (49.47)
Female	53 (56.99)	47 (50.53)
Birth weight (Mean \pm SD)	2.647 \pm 0.423 kg	2.855 \pm 0.561 kg
Birth by SVD	33 (35.48)	41 (44.08)
Birth by LSCS	60 (64.52)	52 (60.22)
Maternal		
Maternal age (Mean \pm SD)	24.05 \pm 3.5 years	26.10 \pm 3.4 years
Rural	28 (30.11)	39 (41.94)
Urban	65 (69.89)	54 (58.06)
Living in flats with low sun exposure	36 (38.71)	43 (46.24)
Primigravida	21 (22.58)	28 (30.10)
Multipara	46 (49.46)	31 (33.33)
Grand multipara	26 (27.96)	34 (36.56)
Hijab & Abaya wearing	49 (52.69)	32 (34.41)
Regular users of cosmetics and sun screens	21 (22.59)	17 (18.28)

p -value>0.05

Mean CRP levels were significantly higher (p -value<0.001) in sepsis group as compared to the control group (table-III).

Vitamin-D deficiency was found in significantly higher number of cases (p -value<0.001) in mothers and their neonates in sepsis group as compared to the mothers and their neonates in control group (table-IV). It was observed that the mean serum vitamin-D levels were significantly lower (p -value<0.001) in the mothers and their neonates in the sepsis group as

cause of sepsis. *Klebsiella pneumoniae* and *Acinetobacter baumannii* were cultured from blood specimens of 03 neonates each. *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* were isolated from 2 neonates each. Methicillin resistant *Staphylococcus aureus* and *Serratia marcescans* was cultured from blood samples of one neonate each. There was one culture positive cases in the control group. *Staphylococcus epidermidis* was isolated from blood sample of one neonate in the control group.

DISCUSSION

The purpose of this study was to establish an association of low maternal serum vitamin-D levels with low serum vitamin-D levels of their term neonates and higher risk of EOS.

In our study, statistically no significant difference was detected (p -value >0.05) between the mothers and their neonates of two groups on the basis of various demographic characteristics. The incidence of EOS in our study was 66.29/1000 live births. Similar results have been shown

was significantly higher (p -value <0.001) in the neonates in sepsis group. CRP was first described by Tillet and Francis in 1930. It is particularly useful in monitoring the response to treatment and in ruling out sepsis. Serial CRP measurements have high sensitivity and almost 100% negative predictive value in ruling out neonatal sepsis^{13,16}.

In this study, serum vitamin-D Deficiency was found in 88.17% mothers and 82.80% neonates in sepsis group as compared to 52.69%

Table-III: Comparison of CRP levels between two groups.

	Sepsis group (n=93)	Control group (n=93)	p -value
Neonates with CRP: ≥ 6 ng/ml n(%)	59 (63.44)	12 (12.90)	<0.001
Neonates with CRP: < 6 ng/ml n(%)	34 (36.56)	81 (87.10)	
CRP Levels (Mean \pm SD)	13.2698 \pm 13.29ng/ ml	2.96 \pm 2.33ng/ ml	
CRP levels range	1.2-96.4 ng/ml	1.0-12.6 ng/ml	

Table-IV: Comparison of number of cases with Vitamin-D Deficiency between two groups.

Vitamin-D (25-OHD) deficiency (<30 ng/ml)	(Number & percentage of cases)			p -value
	Sepsis group (n=93) n(%)	Control group (n=93) n(%)	Total (n=186) n(%)	
Mothers with vitamin-D deficiency	82 (88.17)	49 (52.69)	131 (70.43)	<0.001
Neonates with vitamin-D deficiency	77 (82.80)	37 (39.78)	114 (61.29)	<0.001

Table-V: Comparison of mean maternal & neonatal "vit-D Levels" and culture positivity between two groups.

	Mean vitamin-D levels \pm S.D and Blood culture positive cases		p -value
	Sepsis group (n=93)	Control group (n=93)	
Mother's vitamin-D levels Mean \pm SD	18.16 \pm 8.21 ng/ml	33.35 \pm 12.70 ng/ml	<0.001
Neonate's vitamin-D levels Mean \pm SD	13.93 \pm 13.29 ng/ml	27.92 \pm 7.58 ng/ml	<0.001
Blood culture positivity n(%)	14 (15.05%)	01 (1.08%)	<0.001

in studies from Pakistan and other South Asian countries varying from 14-63/1000 live births¹⁴. The reported incidence of EOS is 0.80-4 cases/1000 live births in high income and 7.1-37.2/1000 in middle income countries¹⁵.

In this study, CRP level was raised in significantly higher number of neonates in sepsis group as compared to control group (p -value <0.001). Moreover, mean CRP level

mothers and 39.78% neonates in control group and the difference was statistically highly significant (p -value <0.001). Overall as aggregate of both groups; 70.43% mothers and 61.29% neonates were vitamin-D deficient. High incidence of vitamin-D deficiency has been reported in various studies done in Pakistan, in the region and worldwide. Hosain *et al* found that 89% of the Pakistani parturient mothers were vitamin-D

deficient¹⁰. Riaz *et al* found that 99.5% of women and 97.3% of neonates were vitamin-D deficient in urban Karachi¹⁷, while Anwar *et al* found 89% of women and 82% of neonates to be vitamin-D deficient in rural Jhelum¹⁸. Even the majority of Pakistani women immigrated to the developed countries like Denmark, Norway and UK have vitamin-D deficiency¹⁹. A review study done by Saeed Akhtar found high prevalence of vitamin-D deficiency in women in India, Pakistan, Bangladesh, and Sri Lanka²⁰. In India, 85.67% neonates and 67-96% pregnant mothers have been found vitamin-D deficient in different communities²¹. Maryam *et al* reported the incidence of vitamin-D deficiency in mothers and their neonates to be 60.2% and 48.9% respectively in Iran²². High prevalence of vitamin-D deficiency has been reported in pregnant women especially the black women and their neonates in Northern USA and Canada²³. Karras *et al* found that 60-84% of pregnant women had vitamin-D deficiency in different areas of Netherlands²⁴. All of these studies also reported a high degree of positive association between the serum vitamin-D levels of mothers and their neonates.

In this study, we found significantly lower mean serum vitamin-D levels in mothers and their neonates in sepsis group as compared to the control group (p -value<0.001). It was evident that the serum vitamin-D level of the neonates is affected by the maternal serum vitamin-D level. Majority of the neonates born to vitamin-D deficient mothers were also vitamin-D deficient. We found high degree of positive correlation between the culture positive sepsis and low maternal and neonatal serum vitamin-D levels. Fourteen neonates (15.06%) were culture positive in the "sepsis group" as compared to just 01 (1.08%) in the "control group". Cetinkaya *et al* in Turkey¹¹, Uday *et al* in India¹² and Lingrong *et al* in China²⁵ have described similar results and reported that a high degree of positive association exists between the vitamin-D levels of mothers and their neonates and that the vitamin-D deficiency in mothers and neonates is a risk factor for neonatal sepsis. Paralak *et al* in Turkey

described a strong positive correlation between maternal serum and umbilical cord 25-OHD levels and that the cord blood vitamin-D deficiency is associated with increased susceptibility to sepsis²⁶. Taha *et al* in their study done in Egypt described that low vitamin-D levels can be sensitive early predictors for EOS in neonates²⁷. McNally *et al* studied the prevalence of vitamin D deficiency in children admitted to the intensive care unit, and found the presence of a high rate of vitamin-D deficiency among critically ill children²⁸. Kempker *et al* reported that even the adult patients with sepsis typically have low vitamin-D levels and vitamin-D status in adults is inversely associated with the severity of sepsis²⁹.

CONCLUSION

Lower maternal serum vitamin-D levels are associated with lower serum vitamin-D levels and higher risk of EOS in their term neonates.

RECOMMENDATION

However, further studies are recommended to find out the effect of vitamin-D supplementation during pregnancy to achieve the sufficient maternal vitamin-D levels and observe for its beneficial effect on vitamin-D levels of their neonates and incidence of EOS.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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