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ORIGINAL RESEARCH

To determine the maternal and neonatal plasma vitamin D levels and the possible effect of the severity of Vitamin D deficiency on early onset sepsis

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Abstract

Background: Neonatal sepsis is characterized by signs and symptoms of infection with or without accompanying bacteremia in the first month of life and is an important cause of morbidity and mortality. The incidence of neonatal sepsis varies between 1 and8 neonates per 1000 live births. Neonatal sepsis may be classified into three groups: early-, late- and very late-onset sepsis. Clinical symptoms are generally subtle, but sepsis may rapidly progress and worsen, and may cause death within a few hours to days

Aims and Objective: To determine the maternal and neonatal plasma vitamin D levels and the possible effect of the severity of Vitamin D deficiency on early onset sepsis

Materials and methods: The cases included all the new borns who presented within 72 hours of age with clinical signs and laboratory findings of early onset sepsis. The controls included all the new borns with no signs of clinical/laboratory infection who aged less than 72 hours and stayed with their mother in the post natal ward. 110 mothers were included in this study, 55 mothers in case group and 55 mothers in control group and 110 neonates, 55 in each group were included.

Results: Present study shows that 24 (43.3%) of mothers had deficient level of 25-hydroxy Vitamin D, while 14(25.4%) had insufficient levels and sufficient levels were found in 30.9% mothers only. While in control group 58.1% mothers has a sufficient levels of of 25-hydroxy Vitamin D while 23.6% had deficiency , 18.1% had insufficient levels respectively. 25-OHD deficiency in study group is statistically significant ($p<0.026$) as compared to control group. 35 (63.63%) of cases have positive blood culture. In culture positive group the most common organism is Burkholderia which is present in 38.1 % of study group followed by Pseudomonas (12.72%), MRSA(7%), Klebsiella (3.6%), E. coli (1.8%) respectively.

Conclusion: Low levels of vitamin D both in the cord blood and maternal blood were significantly associated with neonatal sepsis.

Keywords: vitamin D, neonatal, sepsis

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Introduction

Neonatal sepsis is characterized by signs and symptoms of infection with or without accompanying bacteremia in the first month of life and is an important cause of morbidity and mortality.[1,2] The incidence of neonatal sepsis varies between 1 and8 neonates per 1000 live births.[3] Neonatal sepsis may be classified into three groups: early-, late- and very late-onset sepsis.[3] Clinical symptoms are generally subtle, but sepsis may rapidly progress and worsen, and may cause death within a few hours to days.[4] Early onset sepsis usually presents within first 72 hours[2]. Studies conducted show that the incidence of EOS is 1 to 2 cases per 1000 live birth[3], it manifest as asymptomatic bacteremia, generalized sepsis, pneumonia and/or meningitis. Many diagnostic biomarkers had been studied until now, but none have achieved rapid and reliable identification, specially of infected neonates.[5]Risk factors among mothers which lead to early onset sepsis in newborns are Premature rupture of membrane (PROM) for more than 18 hours, Maternal Diabetes, Pre- eclampsia, chorioamnionitis, Maternal fever more than 38 degree, multiple obstetric procedures, foul smelling liquor, multiple gestation and urinary tract infection.

Vitamin d

Adequate vitamin D status is critically important for the neonates. Vitamin D has immunomodulatory effects on immune function.[6] It was suggested that it might have a role in the optimal functioning of the innate immune system by inducing antimicrobial peptides in epithelial cells, neutrophils and macrophages.[6,9],It also regulates key target genes associated with proper implantation of the placenta. Vitamin D has a direct role in the production of antimicrobial peptides such as cathelicidin, which are produced upon activation of up-regulated vitamin D receptors, require 25(OH)D as a substrate for production, and may play an important role in preventing infection during pregnancy or early childhood[6].

Vitamin D appears to have systemic anti-microbial effects that may be crucial in both acute and chronic infections. Various studies have suggested the association between vitamin D and neonatal immune function.[7] Considerable evidence have linked early vitamin D deficiency with increased risk for fetal growth restriction[6],infection[8]and poor neurodevelopment[9] in later life. Recent studies have implicated vitamin D insufficiency as an important risk factor for neonates and children acquiring infections such as tuberculosis, acute lower respiratory tract infections, pneumonia and influenza. It has been found that newborns level of vitamin D is closely related to maternal vitamin D levels and maternal hypovitaminosis predisposes infants to early onset sepsis. This study will be first of its kind to determine the antimicrobial effect of Vitamin D in early onset sepsis and its correlation with maternal and neonatal vitamin D levels. Cetinkaya et a[8] in his study concluded that lower levels of vitamin D have been associated with increased risk of early onset neonatal sepsis in infants. Sachan et al conducted study in northern India and concluded that there is a high prevalence of vitamin D deficiency among pregnant women and their newborns in northern India.

Aims and Objective

To determine the maternal and neonatal plasma vitamin D levels and the possible effect of the severity of Vitamin D deficiency on early onset sepsis

Materials and Methods

This is a prospective, observational study which was conducted from September 2017 to July 2018. The study is conducted at N.I.C.U of C.R. Gardi Hospital (C.R.G.H) and associated hospital of R. D. Gardi Medical College, Ujjain.

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Inclusion criteria

The cases included all the new borns who presented within 72 hours of age with clinical signs and laboratory findings of early onset sepsis according to the criteria defined by Polinski C et al[1], admitted to NICU of Department of Paediatric Medicine, R. D. Gardi Medical college , Surasa, Ujjain.

The controls included all the new borns with no signs of clinical/laboratory infection who aged less than 72 hours and stayed with their mother in the post natal ward in the Department of Obstetrics and, R. D. Gardi Medical college, Surasa Ujjain.

Exclusion criteria

- Major congenital anomalies.
- Severe birth asphyxia.

110 mothers were included in this study, 55 mothers in case group and 55 mothers in control group and 110 neonates, 55 in each group were included.

Data Collection

A pretested Proforma was used to record the detailed history, clinical findings and investigations. A detailed antenatal history including maternal age, religion, risk factors was obtained from the mother/legal guardians of the baby and from the medical records of the mother. A detailed natal and postnatal history including age at admission, gestational age, gender, type of feeding, pre lacteal feeds and presenting complaints of the neonates was obtained. A detailed physical examination was conducted and the heart rate, respiratory rate, temperature, capillary refill time, color, saturation and a detailed systemic examination was carried out. The gestational age was assessed from the last menstrual period and from New Ballard Score. Blood culture and vitamin D samples were sent for all the recruited patients. 2 ml of blood was obtained from peripheral venepuncture and were sent for relevant investigations including hemoglobin, total leukocyte count, direct leukocyte count, CRP, electrolytes and random blood sugar. Other investigations like chest X ray, lumbar puncture, urine routine and microscopy, urine for fungal hyphae, urine culture and arterial blood gas analysis were done as when required.

Blood Culture

Blood was collected using aseptic technique as per standard procedure. 0.5ml of blood was mixed with 10ml of citrated glucose broth and inoculated as per standard procedure on blood and Macconkey agar. The colonies were examined after 48 and 72 hours.

Vitamin-D

Vitamin D estimation was done using MAGLUMI 25-OH VITAMIN D Kit manufactured by Snibe diagnostics. The test was performed on MAGLUMI fully-auto chemiluminescence immunoassay (CLIA) analyser at Kothari Diagnostic center, Bhopal.

The MAGLUMI 25-OH VITAMIN D assay uses a two incubation chemiluminiscence immunoassay for the quantitative estimation of vitamin D in human serum.

1st incubation: 25-OHD is dissociated from its binding protein by a displacing reagent and binds to 25-OHD antibody forming an antigen- antibody complex.

2nd incubation: 25-OHD coated microleads are added, and then the solid phase binds to the unbound 25-OHD antibodies. The unbound material is removed during a wash cycle. Subsequently a starter was added to initiate a flash reaction. The resultant chemiluminiscent reaction is measured as relative light units (RLUs). An inverse relationship exists between the amount of 25-OH vitamin D and RLUs.The analyser automatically calculates vitamin D

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levels in each sample by means of a caliberation curve which is generated by a 2 point caliberation master curve procedure. The results are expressed in ng

Data analysis

Data was entered in EpiData Entry (Version 3.1, EpiData Software Association, Odense, Denmark) and statistical analyses was performed using Stata (Version 13.0, Statacorp. Texas, USA). Analyses of 25-OH cholecalciferollevels in control group were (mean ± s.d.) for continuous data with normal distribution, median and interquartile range (median (IQR)) for continuous data with non-normal distribution and frequencies and percentages for quantitative data. The differences between groups were evaluated using X2 tests for qualitative data and t-test for independent sample for continuous data with normal distribution .Pearson correlation was used to evaluate the relation between maternal and neonatal 25-OHD. Continuous variables were reported as mean while categorical variables were given as the number or the percentage of newborns with the characteristic of interest. A p-value < 0.05 was considered statistically significant. Statistical analysis was performed using STATA 10.0.

Results

Table 1: Distribution of Study Population

Category	Cases	Control
Males	28 (50.90%)	30 (54.5%)
Females	27 (49.09%)	25(45.4%)
TOTAL	55 (100%)	55 (100%)

Total 110 newborns were enrolled out of which 55 were cases and 55 were control. Out of 55 cases, 28(50.90%) were Males and 27 (49.09%) were Females and in control 30 (54.5%) were Males and 25 were Females (45.4%).

Table 2: Distribution of the Newborns according to Religion

Religion	Case	Control
Hindu	46(83.6%)	45(81.8%)
Muslim	9 (16.3%)	10 (18.1%)
Total	55	55

Majority of population in the present study were Hindu in both cases 46(83.6%) and control 45(81.8%), showing Hindu predominance in this area.

Table 3: Distribution of the Newborns according to Rural and Urban Population

Address	Case	Control
Rural	36 (65.4%)	35 (63.6%)
Urban	19 (34.5%)	20 (36.3%)
Total	55	55

This table shows that in present study maximum population belonged to rural area in both cases 36(65.4%) and control 35(63.6%) as RD Gardi Medical College is situated in rural area.(Surasa village)

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Table 4: Distribution of the Newborns according to Birth weight

Weight	Cases	Controls
<=2.5	15 (27.27%)	23 (41.8%)
>2.5	40 (72.7%)	32 (58.1%)
Total	**55**	**55**

This table shows that in both cases 40(72.7%) and control 32 (58.1%) , weight of newborns were more than 2.5 kg

Table 5: Distribution of the Newborns according to Birth-Weight (<2.5kg)

	Cases(n=15)	Control(n=23)
ELBW	2(3.6%)	0
VLBW	4 (7.2%)	5 (9.09%)
LBW	9(16.3%)	18 (32.7%)
Total	15	23

This table shows that there are only 2 ELBW (3.6%) in cases and nil in control, while VLBW are 4 (7.2%) in cases and 5(9.09%) in controls.

Table 6: Distribution of the Newborns according to Gestational Age

	Cases(n=55)	Control(n=55)
Term SGA	9 (16.3%)	6 (10.9%)
Term AGA	31 (56.3%)	28 (50.9%)
Preterm SGA	6 (10.9%)	5 (9.09%)
Preterm AGA	9 (16.3%)	16 (29.09%)

This Table shows that maximum newborns in present group in both cases 31 (56.35%) and controls 28(50.9%) were Term AGA

Table 7: Distribution of the Newborns according to Maternal education

	Cases(n=55)	Control(n=55)
Educated	34 (61.8%)	37(67.2%)
Uneducated	21 (38.1%)	18(32.7%)
Total	55	55

This table shows that in both cases 34(61.8%) and Control 37(67.2%) mothers were educated (Educated means minimum of Primary education)

Table 8: Distribution of the Newborns according to Level of Education in mothers

	Study group(n=55)	Control (n=55)
Primary	18 (32.7%)	19 (34.5%)
Secondary	12 (21.8%)	15 (27.2%)
Graduate	4 (7.2%)	3 (5.4%)

Table 9: Distribution of the Newborns according to Maternal Age

	Study group(n=55)	Control(n=55)
<20 years	9 (16.3%)	12 (21.8%)
20-30 years	37 (67.2%)	32 (58.1%)
>30 years	9 (16.3%)	11 (20%)
Total	55	55

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This table shows that maximum mothers in our study populations in both cases 37(67.2%) and controls 32 (58.1%) belonged to age group 20-30 years.
Mean maternal age in study group is 24.4 years and 26.1 years in control group.

Table 10: Distribution of the Mothers according to Gravida

	Study group(n=55)	Control (n=55)
Primi	28 (50.9%)	26 (47.27%)
Living(>1)	27 (49.09%)	29 (52.72%)
Total	55	55

This table shows that in present study there is almost equal distribution of Primi mothers and mothers having more than 1 living in Cases 28(50.9%) and controls 26 (47.27%)
This table show that maximum newborns in both study group 37(67.2%) and control 35(63.6%)were born by Spontaneous vaginal delivery.

Table 11: Comparison of maternal risk factors

Maternal risk factors	Cases(n=55)	Control(n=55)
Fever	4 (7.2%)	1 (1.8%)
PROM	8 (14.5%)	0
Pre-eclampsia	3 (5.4%)	3 (5.4%)
Hypertension	3 (5.4%)	4 (7.2%)
APH	2 (3.6%)	0
Anemia	6 (10.9%)	5 (9.09%)
None	29 (52.7%)	42 (76.3%)
Total	55	55

This table shows that in study group 52.7% mothers did not have any risk factors while 47.3% mothers have risk factors in which PROM (14.5%) is the most common risk factor followed by anemia (10.9%), fever(7.2%) ,Pre eclampsia(5.4%) and hypertension (5.4%)respectively. While in control group 76.3% mothers doesn't have any risk factors while in 23.7% mothers risk factors are present in which anemia (9.09%) is the most common risk factor.

Table 12: Distribution of study group and control according to Mother's 25 -hydroxy Vitamin D level

Present study shows that 24 (43.3%) of mothers had deficient level of 25-hydroxy Vitamin D, while 14(25.4%) had insufficient levels and sufficient levels were found in 30.9% mothers only. While in control group 58.1% mothers has a sufficient levels of of 25-hydroxy Vitamin

	Cases(n=55)	Control(n=55)	p- value
Deficiency	24 (43.3%)	13 (23.6%)	0.026
Insufficient	14 (25.4%)	10 (18.1 %)	0.356
Sufficient	17 (30.9%)	32 (58.1%)	0.004
Total	55	55	

D while 23.6% had deficiency , 18.1% had insufficient levels respectively.
25-OHD deficiency in study group is statistically significant ($p<0.026$) as compared to control group.

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Table 13: Distribution of study group and control accordingto newborn 25-hydroxy Vitamin -D level

	Cases(n=55)	Control(n=55)	p- value
Deficiency	41 (74.5%)	21 (38.1%)	<0.001
Insufficient	7 (12.7%)	18 (32.7%)	0.012
Sufficient	7 (12.7%)	16 (29.09%)	0.035
Total	55	55	

This data shows that (74.5%) of newborns had deficient level of 25-hydroxy Vitamin D in study group as compared to 38.1 % in control. 12.7% newborns had insufficient levels in the study group as compared to 32.7% in control. 12.7% newborns had sufficient levels in study group as compared to 29.09% in control group. 25-OHD deficiency in study group is statistically significant (p<0.001) as compared to control group.

Table 14: Mean 25-OH cholecalciferol in newborns with culture positive and in culture negative sepsis group

	Culture positive	Culture negative	P value
Mean 25-OH cholecalciferol level	12.6ng/ml(±6.04)	15.8ng/ml(±5.2)	p=0.467

The mean 25-OH cholecalciferol in newborns with culture positive sepsis was 12.6ng/ml(±6.04) and in culture negative sepsis group it was found to be 15.8ng/ml(±5.2)

Table 15: Distribution of different parameters of Sepsis screen In study group

Parameters	Study group(n=55)
WBC count(<5000/mm3)	15 (27.27%)
ANC(<1500/mm3)	8 (14.5%)
IT ratio(>0.2)	12 (21.8%)
CRP positive	50 (90.9%)

All the parameters of sepsis screen are not positive in study group and the most sensitive indicator is CRP which is positive in (90.9%) , followed by WBC count (27.7%) and IT ratio(21.8%) and the least common indicator of sepsis screen is ANC which is positive in only 14.5 % of study group.

Table 16: Distribution of blood culture in Study group

Blood culture	Cases
Positive	35 (63.63%)
Negative	20 (36.3%)
Total	55

This table shows that 35 (63.63%) of cases have positive blood culture .

Table 17: Bacteriological profile of the Study group

Organism	n=35
Burkholderia	21 (38.1%)
Pseudomonas	7 (12.72%)
MRSA	4 (7%)
Klebsiella	2 (3.6%)
E. coli	1 (1.8%)

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In culture positive group the most common organism is Burkholderia which is present in 38.1 % of study group followed by Pseudomonas (12.72%), MRSA (7%), Klebsiella (3.6%), E. coli (1.8%) respectively.

Discussion

Neonatal sepsis is a clinical syndrome characterized by signs and symptoms of infection with or without accompanying bacteremia in the first month of life.[4] Sepsis is the commonest cause of neonatal mortality; It is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.[3] The incidence of neonatal sepsis according to the data from National Neonatal Perinatal Database (NNPD, 2014) is 38 per 1000 live births.[10]

Neonatal mortality is an important indicator and is included in infant mortality. On account of improved neonatal care and NRHM programme (SNCU, newborn corner) neonatal mortality has reduced to 25.4/1000 live births. According to NFHS 4 data survey Infant mortality rate (IMR) has reduced from 57 to 41 per thousand live births. Neonatal sepsis is defined as a clinical syndrome of bacteremia with systemic signs and symptoms of infection in the first 4 weeks of life.[4]Infants with early onset sepsis usually present with respiratory distress and pneumonia. The source of infection is generally the maternal genital tract.

There are many factors which make newborns susceptible to infection. A newborn is born with immature innate immunity system like reduced phagocytic and opsonisation activity, low complement levels, immature cell mediated and humoral immunity,[11]poor barrier to infection- fragile immature skin easily susceptible to invasion of organism ,immature mucosal barriers and reduced levels of secretory immunoglobulins ,immature ciliary function with reduced ability to clear secretions and poorly developed blood brain barrier make the newborns susceptible to infections more than at any other age. Various risk factors seem to be associated with early onset sepsis. They are-Low birth weight (<2500 grams) or prematurity , febrile illness in the mother with evidence of bacterial infection within 2 weeks prior to delivery, foul smelling and/or meconium stained liquor, rupture of membranes >24 hours , single unclean or > 3 sterile vaginal examination(s) during labor , prolonged labor , perinatal asphyxia (Apgar score <4 at 1 minute) etc.[11]

In the present study the total newborns enrolled were 110, out of them 55 were cases and 55 were controls. The study group consisted of newborns who were clinically suspected to have an infection within the first 3 postnatal days of life, the controls were healthy newborns aged less than 72 hours and stayed with their mother in the post natal ward due to maternal factors.

Out of 55 cases males (50.90%) and females (49.09%) were of equal distribution. Among the control group 54.6% were males and 45.4% were females. Control group showed male predominance.

The study conducted by Cetinkaya et al[8] had a sample size of 100 with 50 cases and an equal number of controls showed almost equal distribution of males among study group(52%) and control(58%) as in the present study. In the study group 67.2% mothers were between 20-30 years and 58.1% mothers in control group were between 20-30 years. So mean maternal age in study group is 24.4 years and 26.1 years in control group. Similarly study conducted by Cetinkaya et al[8] also found the maternal mean age is 26.8 years in study group and 28.4 years among the controls, which is higher than the present study group.

67.2% of newborns were delivered by spontaneous vaginal delivery while 63.6% newborns were delivered by spontaneous vaginal delivery in control group. Similar findings were noted in the study done by Philip T et al [12] in Egypt and found that 68% newborns were delivered by spontaneous vaginal delivery. Similarly Cetinkaya et al[8] found that 60% of newborns were delivered by spontaneous vaginal delivery.

In the present study, 47.3% mothers had associated risk factors for early onset sepsis, the various risk factors were PROM (14.5%) followed by fever(7.2%) ,pre eclampsia(5.4%) and

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hypertension (5.4%)respectively. While in control group 23.7% mothers had associated risk factors for early onset sepsis. Similar study was conducted by TahaSoliman[39] he found that 52% mothers had associated risk factors for early onset sepsis among study group and 20% in control group. Birgul et al [13] conducted a study in which 42.8% mothers have maternal risk factors among study group and 38.4% in control group. Risk factors in the control group in the present study has considerably reduced from Brigul et al study (23.7% vs 38.4%) because of early prevention, detection of risk factors and early referral of pregnant mothers for institutional deliveries.

In the study group (n=24) 43.3% mothers had25-OH cholecalciferol deficiency while only (n-13) 23.6% mothers had deficiency of 25-OH cholecalciferolin control group and this data is highly statistically significant(p-0.026). 25.4% mothers (n=14) in the study group have insufficient levels while only 18.1% (n=10) mothers in control group have insufficient levels this data is highly statistically significant (p-0.026). 17 (30.9%) mothers in the study group have sufficient levels of 25-OH cholecalciferol while (n-32) 58.1% mothers in control group had sufficient level and this data is highly statistically significant (p-0.004). In a study done by Sachan et al[6] on pregnant women in northern India hypovitaminosis D was found in 84% of women. Similarly study conducted by Philip T et al [12] found that 63% of mothers in study group were 25-OH cholecalciferol deficient and 20% were insufficient, while in controls, 26% mothers were 25-OH cholecalciferol deficient and 10% were insufficient .

Gad GI et al[14] et al conducted a study to evaluate the diagnostic value of anti-microbial peptide (cathelicidin), LL-37, in congenital pneumonia and its relation to 25-hydroxycholecalciferol (25-OHD) status. The study included 30 neonates with congenital pneumonia and culture proven sepsis admitted to neonatal intensive care unit of Ain Shams University and 30 healthy neonates as control group. Neonates with congenital pneumonia had significantly higher serum cathelicidin and lower serum 25(OH)D compared to controls**.** Cut-off value of cathelicidin to diagnose congenital pneumonia was 17 pg/mmol with 93% sensitivity and 86% specificity. Neonates with congenital pneumonia had significantly high cathelicidin and low 25(OH)D suggesting a possible role of fetal 25(OH)D deficiency as predisposing factor for congenital pneumonia.

It has been reported by Chin et al.[15] that higher vitamin D levels in pregnant women was associated with a lowered rate of Group B Streptococci vaginal carriage. Levels of vitamin D in cord blood at birth was measured and was found to be deficient (<10 ng/ml), insufficient (10 to 30 ng/ml), or normal (>30 ng/ml) in 32.1%, 53.0% and 14.9% of tested subjects, respectively. The percentage of GBS vaginal carriage was 15.4. A negative association was observed between GBS vaginal carriage and level of vitamin D ($P < 0.01$). Thus it was concluded that the correct vitamin D level was associated with a lower rate of GBS vaginal carriage during pregnancy. In the study group of present study 63.63 % of newborns had a positive blood culture and the most common organism in the present study came out to be Burkholderia(38.1%) followed by pseudomonas(12.72%) and MRSA(7%).

Many studies reported that, during infancy, low concentrations of cord blood 25-OH vitamin D had been associated with increased incidence of sepsis in the first year of life and available evidence suggested that 25-OH vitamin D deficiencies may be a predictor of sepsis and/or elevated mortality rate in critically ill patients, and its deficiency is strongly associated with the risk of blood culture positivity [16]. The proposed mechanism is that defects in macrophage functions and the production of pro-inflammatory cytokines may occur in 25-OH Vitamin D deficiency.

Burkholderiacepacia was isolated four times from clinical specimens in Neonatal Unit (NU) of Southern Health-Monash Medical Centre, Clayton, Victoria, Australia. The mean 25-OH cholecalciferol in newborns with culture positive sepsis was 12.6ng/ml(±6.04) and in culture negative sepsis group it wasfound to be 15.8ng/ml(±5.2). In the control group mean 25-OH

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cholecalciferol level is 23ng/ml(±2.7). In the broad category of culture positive and culture negative sepsis there was no difference in the mean vitamin D levels (p=0.467). Similarly study done by Cetinkaya et al [8] found that mean 25-OH cholecalciferol in culture positive sepsis is 10.1ng/ml(±1.8) while in culture negative sepsis group is 8.4ng/ml(±3.2).(p-0.25). This is a observation but the data is not statistically significant in both the studies.(p-0.467 vs p- 0.25), though the level of mean 25-OH cholecalciferol is found to be much lower in culture positive group than in culture negative group but data is not statistically significant and will require further study and larger sample size.

Conclusion

Low levels of vitamin D both in the cord blood and maternal blood were significantly associated with neonatal sepsis.

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