"CORD BLOOD VITAMIN A LEVELS IN PRETERMS AND IT'S ASSOCIATION WITH EARLY NEONATAL PERIOD MORBIDITIES- A PROSPECTIVE COHORT STUDY"

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Dr DNYANESH D K M.D., L.L.B
Professor & Head
Department of Pediatrics
J N Medical College
KAHER
Belagavi, Karnataka

Professor & Head
Department of Pediatrics
KLE University
J N Medical College, Belagavi,

Date: 27/06/24
Place: JNMC, Belagavi

Dr N S MAHANTASHETTI M.D.
Principal
J N Medical College
KAHER
Belagavi, Karnataka

PRINCIPAL
JAWAHARLAL NEHRU MEDICAL COLLEGE
BELAGAVI

Date: 27/06/24
Place: JNMC, Belagavi

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(A constituent unit of KLE Academy of Higher Education & Research Deemed-to-be-University)

(Recognized by National Medical Commission, New Delhi)

Accredited 'A+' Grade by NAAC (3rd Cycle) **Placed in Category 'A' by MoE (GoI)**

Nehru Nagar, Belagavi- 590 010, Karnataka, INDIA

0831 – 2471350 0831 – 2470759 www.jnmc.edu rincipal@jnmc.edu

Ref No: MDC/PG/ Date: 25-06-2024

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Dr. (Mrs.) N.S. Mahantashetti.
Chairperson-Antiplagiarism Committee &
Principal,
J. N. Medical College, Belagavi.

To,
Reg. No. BM0121019
Postgraduate Student,
2021-22 Batch,
Department of Paediatrics
J. N. Medical College, Belagavi.

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K.L.E. ACADEMY OF HIGHER EDUCATION AND RESEARCH
(Deemed – to- be- University)
Accredited 'A+' Grade by NAAC in (3rd Cycle) Placed in Category 'A' by MHRD (GoI)
JNMC INSTITUTIONAL ETHICS COMMITTEE
JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRU NAGAR, BELAGAVI-590010 (KARNATAKA-INDIA)
Website: http//www.jnmc.edu
E-Mail : dome@jnmc.edu
Phone: (+ 91-(0)831 Office : 2472550
Principal: 2471701
Fax No. +91 (0)831 – 2470759

Ref No.MDC/JNMCIEC/91 **Date: 03/10/2022**

To,

REG NO. : BM0121019
PG Student in Paediatrics,
J. N. Medical College,
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

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(Dr. Nayana Hashilkar)
Basic Medical Scientist & Alternate Chairperson
JNMC Institutional Ethics Committee
J.N.Medical College, Belagavi.

(Dr. Harsha Hegde)
Chairman,
JNMC Institutional Ethics Committee
J.N.Medical College, Belagavi

LIST OF ABBREVIATIONS

RDS	-	Respiratory distress syndrome
WHO	-	World Health Organization
LBW	-	Low Birth Weight
VLBW	-	Very Low Birth Weight
ELBW	-	Extremely Low birth weight
RBP	-	Retinol Binding Protein
ERG	-	Electroretinogram
ROP	-	Retinopathy of prematurity
RDR	-	Relative dose response
SGA	-	Small for Gestational Age
UCB	-	Umbilical cord blood
ELISA	-	Enzyme linked immunosorbent assay
CPAP	-	Continue Positive Airway Pressure
HMD	-	Hyaline membrane Disease
LSCS	-	Lower segment caesarian section
NVD	-	Normal Vaginal Delivery
µmol/L	-	Micromole per litre

ABSTRACT

Background and objectives:

Vitamin A, a fat soluble vitamin, plays an essential role in early lung and airway tissue differentiation and the retina. Vitamin A also maintains epithelial integrity, bone development, immunity and promotes the maturation of type 2 alveolar epithelial cells. Vitamin A aberration is associated with diseases such as night blindness, corneal ulcers, dry eye, immune dysfunction and respiratory infections. Several studies have reported vitamin A insufficiency to be associated with morbidity of premature infants. Preterm neonates born with low vitamin A levels may have increased risk of developing respiratory distress syndrome, hyperbilirubinemia, sepsis. According to WHO's guidelines on newborn care, it is suggested that infants should receive single oral dose of Vitamin A within first 48 hours after birth to prevent Vitamin A deficiency. This study examines umbilical cord blood to determine Vitamin A levels, also to explore the association of cord blood retinol levels in preterms with early neonatal period health problems.

Materials and methods:

All neonates who were born in the labour room of KLES Dr. Prabhakar Kore hospital and who were born within the 37-week period of gestation were taken in the study. Written consent taken from the parents of newborns who fulfilled the inclusion criteria after the researchers had explained the purpose of the study to them. All of the information on the neonate, included the gestational age, gender, birth weight, data of resuscitation, and APGAR scores, was recorded into a structured proforma. The

neonates included in the study were followed up till 7 days of life that is early neonatal period and these parameters were recorded:

At the time of admission, Clinical grading of Respiratory distress in the preterm neonates was done by Modified Downe scoring system. Diagnosis of Respiratory distress syndrome was done by Clinical and Chest X ray findings.

All neonates with respiratory distress were followed up for the requirement of Surfactant administration, mode of respiratory support required like Mechanical Ventilation, CPAP, oxygen supplementation through Nasal prongs and its duration respectively.

Hyperbilirubinemia that is bilirubin levels requiring phototherapy was recorded Presence of Sepsis based on blood culture growth was recorded.

Results: Majority of preterm infants have low vitamin A levels, with 72.22% in low category compared to 27.78% with normal levels. No significant difference in birth weight($p=0.668$) or gestational age among groups ($p=0.539$). Significant association with vitamin A levels ($p < 0.001$); higher deficiencies in LSCS deliveries. No significant differences in APGAR scores at l and 5 minutes across vitamin A levels ($p=0.423$ and $p=0.390$, respectively). Significant association of respiratory distress with vitamin A levels ($p<0.001$); higher Modified Downe scores associated with lower levels of Vitamin A. Significant association with vitamin A levels; higher deficiencies required more oxygen support , more CPAP and ventilator support for longer duration($p=0.048$). None of the infants with normal vitamin A levels required surfactant while 14.29% with deficiency and 15.69% with severe deficiency required surfactant therapy. Significant association with cord blood vitamin A levels ($p = 0.005$); higher deficiencies had more RDS cases; surfactant need and X ray changes

found more in low Vitamin A group. Sepsis did not show significant difference (p=0.086) although it was more prevalent in low vitamin A group. Significant correlation with cord blood vitamin A levels (p = 0.024); higher deficiencies had more hyperbilirubinemia cases.

Conclusion

The study reveals a significant prevalence of vitamin A deficiency among preterm neonates, showing more than half of the infants with severe deficiency. Key findings indicate that lower umbilical cord blood (UCB) vitamin A levels are significantly associated with increased risk of RDS, hyperbilirubinemia, and the need of extended oxygen therapy, CPAP support and longer duration of ventilator support.

Keywords: *Vitamin A levels, preterms, respiratory distress syndrome*

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INTRODUCTION

Preterm infants have elevated rates of morbidity, including apnea, respiratory distress, kernicterus[1], and mortality, as comparison to term infants[2,3].

Vitamin A, a lipid-soluble vitamin, has a crucial function in the early development of lung and airway tissues as well as the retina. Vitamin A has an important role in preserving structure, function in epithelial tissues, supporting growth and strength of bones, enhancing the immune system, and facilitates growth of type 2 alveolar epithelial cells. Vitamin A deficiency is linked to conditions such as nyctalopia, corneal ulcers, xerophthalmia, impaired immunological function, as well as respiration infections. Multiple studies have indicated that lack of Vitamin A is linked to health problems in preterm newborns. Preterm infants with low Vitamin A levels may be at risks of suffering Respiratory distress syndrome (RDS), hyperbilirubinemia, sepsis, also systemic inflammatory response syndrome.[4]

Insufficient levels of serum retinol heighten the likelihood of severe respiratory distress syndrome also negative pulmonary consequences, like bronchopulmonary dysplasia, among premature newborns weighing less than 1250 g or born before 29 weeks of gestation[5]. In addition, Esteban-Pretel et al. have proposed that a lack of Vitamin A can have a negative impact on the functioning of the alveoli and raise the likelihood of developing lung illness[6]. Preterm newborns with inadequate Vitamin A levels are more likely to develop chronic lung disease and hyperbilirubinemia[7,8]. Furthermore, a lack of Vitamin A can diminish defenses enhancing permeability at intestinal lining[9,10]. Nevertheless, the administration of Vitamin A can improve the damage to the intestinal lining caused[11-13]. Low levels of

Vitamin A in blood can potentially raise the chances of Respiratory distress syndrome and negative pulmonary outcomes for newborns with very low birth weight[5,14].

However, additional research is necessary to provide further clarification on this matter. Vitamin A has the ability to control both particular and non-specific immune responses, and it can also serve as an antioxidant to defend against bacterial infections.

NEED FOR THE STUDY:

Our study is based on the premise assuming decreased levels of Vitamin A in umbilical cord blood can lead to an increase in preterm morbidities. According to WHO's guidelines on newborn care, it is suggested that infants should receive single oral dose of Vitamin A within first 48 hours after birth. This recommendation aims to prevent Vitamin A deficiency. This study examines umbilical cord blood to determine Vitamin A levels, also to explore the association of cord blood retinol levels in preterms with early neonatal period health problems.

OBJECTIVES

PRIMARY OBJECTIVE: To explore the association between umbilical cord blood Vitamin A levels in preterms and early neonatal period morbidities.

SECONDARY OBJECTIVES:

1) To determine prevalence of low Vitamin A levels in preterms.
2) To analyze the potential factors that might affect umbilical cord Vitamin A levels.

REVIEW OF LITERATURE

Vitamins are a collection of organic substance families that are chemically distinct from one another and cannot be manufactured by humans. Vitamins are essential for maintaining a healthy metabolism and must be included in the diet in smaller quantity. Two categories in this group are fat soluble and water soluble type. The intake of liver was recognised by the ancient Egyptians as a potential treatment for night blindness[14]. In the late 1920s, a Swiss researcher by the name of Karrer and his colleagues were successful in isolating the fat-soluble substance that was found in liver, and they gave it the name Vitamin A. Preformed Vitamin A, also known as retinols, can be obtained from a variety of foods, the most frequent of which being butter, liver, egg yolk, and kidney. The majority of beta-carotene, or Vitamin A's provitamin, is present in carrots, sweet potatoes, green leafy vegetables. The preformed state of Vitamin A is present in animal sources or supplementation whereas the form of Vitamin A that comes from plant sources is pro Vitamin A.

According to WHO's guidelines on newborn care, it is suggested that infants should receive an oral dose 50,000 international units of Vitamin A before 48 hours of delivery. This recommendation aims at preventing Vitamin A deficiency, which is crucial for reducing the risk of visual impairment and enhancing immune function during infancy and childhood.[15]

PRETERM BABIES

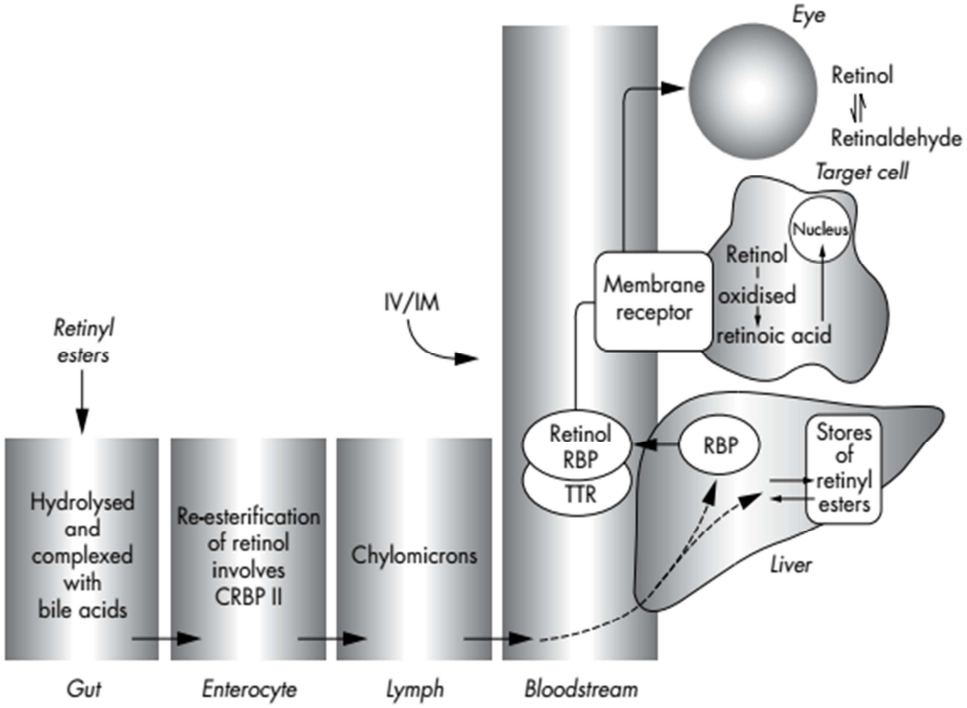
Unfortunately, it is not possible to assume that premature children would have sufficient Vitamin A. This significant segment of newborns is seen to have insufficient reserves of retinol in their bodies; frequently not able to accept

supplements orally as a matter of course, and is predisposed to conditions affecting gastrointestinal tract, respiratory system and eyes. In comparison to term neonates, preterm neonates are seen to have lower plasma concentrations of both retinol as well as retinol binding protein. This is because preterm newborns have lower hepatic reserves than term infants. Plasma concentrations of retinol continue to be low throughout an infant's initial year, especially in premature neonates who are the products of multiple births. This is notably true in infants who were born prematurely. Since at least the year 2000, these problems have been identified. However, preterm children, especially ones with ELBW, continue to be at danger of Vitamin A insufficiency since the ideal intake needed or the guidelines to monitor Vitamin A status have not been adequately defined. This puts preterm newborns at risk of retinol deficiency. [16]

UPTAKE AND METABOLISM OF VITAMIN A

Retinol, retinoic acid, retinaldehyde are among the substances referring to Vitamin A. You can get retinol in two ways: either directly from foods that come from animals or by making it yourself through the breaking down of beta-carotene. The way retinyl esters are absorbed from food is a complicated process that requires hydrolysis and formation of bile acid complexes in gut lumen before they are absorbed by enterocytes. The availability of cellular RBP type 2, which is required for the metabolism of Vitamin A inside cells and the further transport of Vitamin A into the lymphatic system, may be limited in preterm infants. Preterm infants are therefore more likely to have low levels of Vitamin A in their blood. Following absorption, retinol is coupled to retinol binding protein in the liver, and this complex is then transported in plasma as the retinol-retinol binding protein complex, which is bound to transthyretin (1:1ratio). The active metabolite, retinoic acid, is produced when the

retinol that is circulating in the bloodstream binds to a particular membrane receptor and is then transported to the tissues that need it. The particular methods by which retinoic acid impacts the activity of intracellular components are difficult to describe and are not fully understood. The liver is responsible for storing around 90 percent of body's reserve of Vitamin A as retinyl esters. The lung, the eye also important locations for the storage of Vitamin A. Retinaldehyde is produced when Vitamin A undergoes reversible oxidation in the retina, which results in the formation of a second active metabolite. The visual pigment rhodopsin contains retinaldehyde, which is an essential component of the molecule. When retinaldehyde undergoes photoisomerization in response to light, a phototransduction cascade is initiated, which is the initial step in the process of vision. [16]



"Figure 1 Uptake and metabolism of Vitamin A. C-RBP II, Cellular retinol binding protein type 2; IV, intravenous; IM, intramuscular; RBP, retinol binding protein; TTR, transthyretin." [16]

"FUNCTIONS OF VITAMIN A IN THE PRETERM NEONATE"

Respiratory functions

Both cellular differentiation as well as the production of surfactant in the fetus's lung are dependent on the presence of Vitamin A during the development period. Third trimester is when the lungs accumulate a large amount of Vitamin A. As the lungs continue to develop and thrive, these stores are quickly drained in the perinatal period. The effects of retinol and steroid hormones on lung growth in prenatal and postnatal period are comparable, they function with the help of similar cell receptors, which might be dependant on one another. The pathological alterations that occur in chronic lung illness are comparable to those that are seen in experimental animals with low retinol levels. In premature newborns with bronchopulmonary dysplasia, the amounts of plasma retinol were low, and the amount of hepatic reserves was reduced. The fact that this is the case lends credence to the theory that a lack of Vitamin A is a factor in development of chronic lung disease and infections of the respiratory tract in these newborns. Investigations of supplemental Vitamin A that were either observational or randomized produced outcomes that were different from one another. This was attributable to a combination of circumstances, such as the restricted number of subjects, post delivery steroid use, and the diversity in ventilation care, baseline retinol status, and supplementation plans. Each of the two categories of studies were carried out on adults. [17-23] It was demonstrated by Tyson et al.[24] that "providing injectable Vitamin A (5,000 lU of Vitamin A intramuscularly thrice per week for 28 days) to ELBW infants as early as second day of life lessens the chances of chronic lung illness at 36 weeks of age and also reduces the lab evidence of retinol insufficiency." Therefore, a marginal yet substantial decrease in the morbidity,

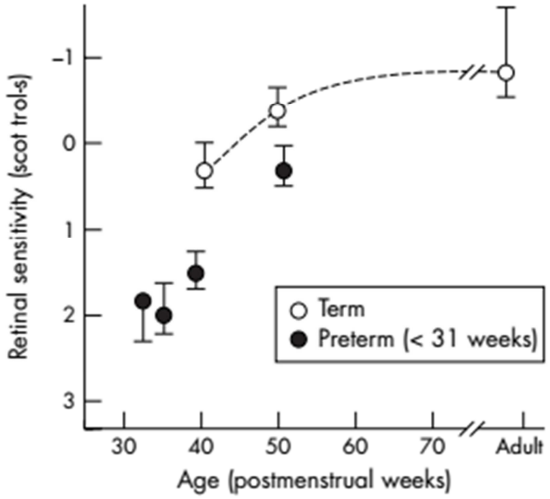
mortality or dependence on oxygen in the first thirty days of life in premature newborns those were given injectable Vitamin A as a supplement was seen.[16]

It is impossible to assess the pulmonary reserves of Vitamin A in preterm newborns in vivo, and the results obtained postmortem may not accurately reflect the condition as it existed in life.. It is likely that a preterm newborn's lungs are deficient in retinol at the time of delivery; however, it is questionable if this may be changed by supplementing the mother or the neonate and whether or not this can be done. As far as we are aware, there is no correlation between levels of retinol in the plasma with amounts of Vitamin A in the lungs, assuming there is any correlation at all. Intramuscular supplementation did not result in substantial increase in pulmonary Vitamin A reserves in a specific sample of neonates who were born with exceptionally low weight. In inflammatory diseases of the lungs, research conducted on both animals and adults has demonstrated an increase in Vitamin A consumption as well as a depletion of hepatic reserves.[16]

Visual function

Insufficient levels of Vitamin A, which is also an essential component of visual pigment (and, as a result, of the developing rods, cones), prevent the anterior section of the eye from functioning properly. Vitamin A is also necessary for the development of photoreceptors. The condition known as xerophthalmia is a manifestation of the deficit in older kids. There are a number of indications and symptoms associated with this illness, some of which include keratomalacia, corneal ulcers, and night blindness. The association between preterm birth and Vitamin A status has not been explored, despite the fact that microscopic conjunctival abnormalities in preterm newborns that are compatible with Vitamin A insufficiency

have been seen. Retina in a preterm newborn contains much less rhodopsin when compared to the retina of a term-born infant at birth; it is unknown how quickly rhodopsin is further accreted, and it is also uncertain if it is connected to the total body retinol stores. When a child is exposed to light at a younger age, amount of rhodopsin that is present in the developing retina is reduced. This is because the amount of rhodopsin is dependent on availability of retinol. An impaired ability to adapt to dark environments is one of the initial indicators of retinol deficiency, which is dependent on adequate levels of retinol in retina. Vitamin A levels of retina are a critical factor in determining the intensity of dark-adapted (rods) retinal sensitivity. Electrophysiological measurements can be taken to determine the sensitivity of rod photoreceptors, and the results of these measurements are found to coincide with the outcomes of subjective assessments. When a woman is between 30 and 50 weeks postmenstrual, her electroretinogram (ERG), which measures the sensitivity of her retina, shows a significant increase. Additionally, some preliminary evidence suggests that there is a correlation between retinal sensitivity in premature newborns and liver reserves of retinol. This increase occurs when the woman is between 30 and 50 weeks postmenstrual. It is not clear why the dark-adapted retinal sensitivity of premature neonates at term corrected gestational age is lower when compared to term neonates, as shown in figure 2. Despite this, it is the case that this is the case. [16]



"Figure 2 Increase in retinal sensitivity with age (retinal sensitivity defined as the retinal illuminance of the flash which produces a half maximal electroretinogram)" [16]

Both the function of the dark-adapted retina and corneal epithelium are affected by the amount of Vitamin A that is stored in the eye. The ERG is able to provide an objective assessment of the function of the retina and can be used on preterm newborns as early as 31 weeks gestation. Changes in the dark-adapted electroretinogram were observed in subjects who have shortage in Vitamin A. It is possible that the dark-adapted ERG is better in assessing deficiency status compared to plasma retinol. Vitamin A administration is generally capable of reversing ERG abnormalities, with the exception of the most severe cases. Vitamin A insufficiency may be the cause of decreased retinal sensitivity in preterm newborns when their ages are corrected to term.[16]

Some authors also found correlation of low plasma Vitamin A concentrations and development of ROP. The combined data suggest that newborns who received Vitamin A supplements showed trend toward developing retinopathy. Multiple factors

might lead to ROP, one of which is the oxidative damage caused by free radicals to growing retina. This damage may, theoretically, be mitigated by antioxidant properties of retinol. ROP has a detrimental effect on the photoreceptors that are in the process of forming. The risk of developing threshold ROP was 0% in set of ELBW children who were given Vitamin A(10,000IU IM), in contrast to 16% in a group of infants who were given only half of this amount. It appears that larger dosages may have a favourable influence on ROP development, despite the fact that the analysis was not showing statistical significance. [16]

Liver

Relative dose response (RDR) test is used on premature newborns, which enables one to obtain an indirect measurement of hepatic storage while the test is still being performed in vivo. Hepatocytes that are low in Vitamin A readily take it up from the blood after receiving a dosage of it either orally or intramuscularly, and they form retinol- RBP complexes. Calculating RDR can be accomplished through the measurement of either retinol or retinol binding protein. RDR is difference seen in concentration of retinol or retinol binding protein before the dose and the concentration of that same compound in the plasma five hours following administration of the dose. The test is able to differentiate low plasma retinol levels as a result of a lack of Vitamin A (high dose response) or as a result of other reasons (low dose response). It is suggested , low retinol levels in such premature neonates are a reflection of diminished hepatic storage of Vitamin A because the test coincides with retinol levels before the dose in healthy premature neonates. Even when there is a higher retinol levels after intramuscular supplementation, the RDR may still show that there are fewer retinol reserves in the liver. [16]

Cardiovascular system

In the first three months of pregnancy, retinol is essential for development of the cardiopulmonary system, and after birth, Vitamin A speeds up ductus arteriosus contraction. Intramuscular Vitamin A administration did not have an effect on the rate of spontaneous ductus closure in cohort of ventilator-dependent preterm newborns weighing between 500 and 1500 grams. However, the dose that was administered was significantly lower than the one that had demonstrated to improve respiratory outcome. [16]

PLASMA CONCENTRATIONOF VITAMIN A IN PREMATURE NEWBORNS

Plasma concentrations of retinol only reflect body stores when they are in a condition of critical depletion or excess. Supplementing Vitamin A utilised in achieving improvement clinically in those who are deficient in Vitamin A; however, this does not necessarily increase plasma levels. In addition, pharmacokinetics of Vitamin A differ from one infant to the next. Plasma retinol levels might be an indicator of availability of carrier protein which binds to it. Retinol binding protein levels are frequently low in preterm infants. Plasma values in the range of 0.7–2.8 micromol/litre are considered adequate in older children when determining Vitamin A adequacy. Plasma levels of retinol at 0.35 micromol/litre, which is equivalent to 100 mg/l, are believed to be an indication of severe Vitamin A deficiency since they are associated along with diminished liver storage and manifestations of Vitamin A deficiency. A milder biochemical insufficiency in childhood is related with higher morbidity and mortality, even though it may not appear as xerophthalmia. Plasma retinol levels >0.7 micomol/litre suggest Vitamin A sufficiency, according to studies

where Vitamin A supplements were given to preterm newborns; however, evidence got altered because of postnatal drugs usage. The majority of preterm children, even those who are generally healthy, have plasma retinol concentrations of 0.7 micromol/litre. However, twenty percent ELBW babies without supplementation have retinol concentrations of 0.35 micromol/litre by the age of 28 days. However, it is not entirely obvious what this means with regard to the functional status.[16]

Corticosteroid effects

Corticosteroid use both during and after pregnancy causes a significant increase in the retinol levels of premature neonates. According to the available research, giving prenatal steroids may be a factor in higher levels that are reported shortly after delivery in premature neonates. When steroids are administered, there is a substantial increase in serum retinol, which results in a decrease in liver reserves. This is a consequence of the steroids. There was an increase in the liver and pulmonary reserves of retinol among newborns with extremely low birth weight who had taken steroids postnatally. However, restricted sample size, or autopsy findings might not be accurately representative. When it comes to positive pulmonary response that is observed in response to postnatal steroids, there is a good possibility that Vitamin A is responsible for at least some of it. [16]

VITAMIN A SUPPLEMENTATION

It is possible to administer Vitamin A through the intramuscular, intravenous, or enteral route. Vitamin A is well absorbed through the digestive tract in term newborns (with the exception of malabsorptive conditions), and supplemental Vitamin A is normally administered through the digestive tract to infants and children

of all ages. Vitamin A, when administered orally in conjunction with early feedings, has the potential to produce plasma concentrations of retinol that are comparable to those of Vitamin A administered intramuscularly in children in VLBW babies, provided that the oral dosages are suitably liberal. On the other hand, high enteral doses of Vitamin A from birth neither boosts plasma retinol levels nor improve outcomes in ELBW babies. At the very least in the first few days of life, these newborns need to be supplemented with Vitamin A through the parenteral route. This is because they are the ones who are most likely to benefit from receiving more Vitamin A. Vitamin A that is administered intravenously presents a number of challenges. In the presence of light, Vitamin A undergoes degradation, and a large amount of it is absorbed via the intravenous tubing. An increase in the effectiveness of delivery can be achieved by combining Vitamin A with lipid emulsion before infusing; this route of intravenous administration is normally suggested. It is strongly recommended that "the practice of providing a multivitamin preparation in an amino acid/dextrose mix, which is still routinely used in the United Kingdom, be firmly discouraged." [16]

Supplemental Vitamin A is usually administered as Vitlipid N in the United Kingdom, with a recommended dosage of 4 millilitres per kilogramme per day. The amount of Vitamin A that is provided by this is 910 international units per kilogramme per day (280 milligrammes per kilogramme per day), along with vitamins K,E. Even with this plasma retinol levels could not be maintained above 0.7 micromol/litre consistently in seven VLBW babies. After further consideration, the American Society for Clinical Nutrition indicated that a greater dose be evaluated for preterm newborns and recommended that the least dose that is appropriate for them be 910 international units per kilogramme per day. However, there was no discernible

improvement in the clinical outcome of the infants. On the other hand, not all infants were at a considerable risk of developing bronchopulmonary dysplasia, and the number of cases was quite low. It appears from the preliminary findings of this research that the current recommended intravenous dose of Vitamin A supplementation doesn't result in increased Vitamin A plasma concentrations in VLBW babies. There isn't any clarity regarding the ideal intramuscular dose. Some suggest in ELBW newborns 5,000 international units thrice weekly. Although this effectively improves respiratory outcomes in extremely low birth weight children, a significant number of treated newborns still exhibit biochemical indications of poor hepatic reserves and are only able to achieve plasma retinol concentrations that are on the borderline. The administration of intramuscular injections is a painful process, and the logic for administering twelve injections to each and every ELBW newborn for a slightly better short-term respiratory outcome is doubtful. Vitamin A supplementation administered intramuscularly is not generally done, even in the United States, despite the fact that there is evidence that it is beneficial. When compared to enteral administration, parenteral administration of Vitamin A is more effective for the sickest and smallest newborns. However, comparison of intramuscular injection of Vitamin A lipid emulsion to intravenous administration of Vitamin A is not known. There has not been a single published study that has directly compared the delivery of Vitamin A intramuscularly to when given intravenously in very low birth weight babies, with regard to mortality, morbidity, or Vitamin A status. [16]

Once the introduction of enteral feeding has been completed, the majority of neonatal units recommend that preterm children get oral vitamin supplements. However, the doses of these supplements vary and are not typically altered to accommodate the smallest and most immature infants, such as preterms or very low

birth weight neonates. It's possible that a lot of neonatologists who are currently working are unaware of the fact Vitamin A content of "ABIDEC (Pfizer Ltd, Walton Oaks, UK) is cut by two thirds, which means that the recommended dose of 0.3 ml per day only gives 666 international units of retinol." Additionally, the government of Canada has lately approved increased amount of Vitamin A that can be found in preterm formula, 1,420 international units for every 100 kilocalories.[16]

VITAMIN A TOXICITY

It would appear that the majority of the concerns regarding the possible toxicity of Vitamin A are unjustified; yet, this has resulted in preterm newborns receiving lower amounts of the vitamin. There is no data that has been published to suggest that giving preterm infants parenteral supplements of Vitamin A in dosages of up to 8500 international units per kilogramme per day is associated with substantial adverse effects. Even when paired with a bulging fontanelle, the administration of supplemental Vitamin A to bigger newborns during perinatal period is not associated with any deleterious developmental effects. According to the United States Institute of Medicine, tolerable upper intake level for Vitamin A for infants (including neonates) is: 0-6 months: 2000 IU per day [16]

HYPERBILIRUBINEMIA

Neonatal hyperbilirubinemia is clinical problem that we encounter commonly throughout the neonatal period, particularly first seven days 0f life[25,26]. Over eight to eleven percent of neonates will develop hyperbilirubinemia that is clinically severe. When total serum bilirubin in a newborn is higher than the 95th percentile for the age group (high risk zone) during the first 7 days 0f life, the condition is referred to as

hyperbilirubinemia[27,28]. In healthy neonates, it is anticipated that approximately sixty percent to eighty percent may present with idiopathic neonatal jaundice.[29]. Yellowish colouring of skin and sclera that occurs in neonates as a result of bilirubin is referred to as neonatal jaundice[30]. Initially, the icterus is observed in the face of newborns; however, as the bilirubin level rises, the icterus spreads throughout the body and eventually reaches the extremities. During the first week of life, this syndrome is prevalent in between fifty and sixty percent of babies[31]. Race, genetic mutations, acquired and inherited abnormalities, such as hereditary spherocytosis, Crigler Najjar syndrome1 and 2, and Gilbert's syndrome, are the key factors that contribute to increased bilirubin levels. Molecular genetics has demonstrated that there is a connection between newborn hyperbilirubinemia and many genetic variants, each of which has the potential to bring about a change in enzyme activity.

SEPSIS IN NEONATES

Neonatal sepsis is a condition that occurs when an infection of the bloodstream occurs in newborn infants who are in the neonatal phase and are younger than 28 days old. The prevalence of this condition continues to be among primary causes of illness ,mortality among newborns in middle and lower incomes countries [32]. Sepsis in neonates is divided into early-onset and late-onset sepsis. These categories are determined by the time of presentation after delivery. It is regarded to be early onset of sepsis in newborns if it occurs within the first 72 hours of their lives, while sepsis that occurs within the next 72 hours of their lives is considered to be late onset.[33].

Respiratory distress syndromc in Neonates

This condition typically manifests itself within a few hours after delivery, and in many cases, it occurs soon after delivery. It is most commonly preterm neonatal infants who are affected, and term neonates are affected quite occasionally. RDS is a condition that occurs in a manner that is inversely proportional to the gestation of the infant, with more severe cases of the disease occurring in newborns who were born prematurely. Despite the fact that there are therapy methods that have improved the result in these newborns, such as surfactant, prenatal corticosteroids, and advanced respiratory care of the newborn, respiratory distress syndrome (RDS) remains to be a primary cause of mortality and morbidity among preterm newboms..[34]

LITERATURE FROM PREVIOUS STUDIES:

A study was carried out by Tao E and colleagues (2020) with the purpose of investigating the correlation between the amounts of Vitamin A in the umbilical cord blood and the morbidities that were seen in late preterm newborns. Vitamin A was measured by an enzyme-linked immunosorbent test, which was performed on umbilical cord blood samples that were taken shortly after the birth of the infant. When it comes to late preterm infants, the prevalence of low umbilical cord blood Vitamin A levels below 0.7 micromol/Litre was shown to be 37.5%. Comparatively, when compared with vaginal deliveries, caesarean deliveries shown to be related with Vitamin A level in the umbilical cord that was less than 0.7 micromol/Litre (p value < 0.001). Despite this, no correlation between the Vitamin A levels and the gestation age, birthweight, or baby's gender. It was shown that a cord blood Vitamin A less than 0.7 micromol/Litre wasn't an independent risk factor for sepsis, respiratory distress syndrome, hospitalisation, oxygen supplementation, and hyperbilirubinemia.

They came to the conclusion that it is not uncommon for late preterm newborns to have an inadequate amount of Vitamin A in their cord blood. A low level of Vitamin A in the blood of the umbilical cord is connected with deliveries that are performed via caesarean section. Ta et al concluded from their study that "The presence of low amounts of Vitamin A in the umbilical cord blood at birth does not lead to an increase in morbidity in late-preterm infants. This includes respiratory distress syndrome, hyperbilirubinemia, and sepsis."[4]

Adhikari KM et al. (2011) highlighted deficiency conditions in neonates, particularly low birth weight babies, by assessing Vitamin A levels. This was to aid in making recommendations to supplement Vitamin A in these newborns. LBW newborns were significantly affected by these condition. neonates with birth weights ranging from 1505 to 2455 grams were included in the study, and 154 of these low birth weight neonates were subjected to an High Performance Liquid Chromatography analysis to determine plasma Vitamin A (retinol). Additionally, samples were taken from fifty-five neonates who had a normal birth weight. In the study, low birth weight (LBW) infants were separated into two distinct categories: preterm LBW and LBW-term but small for gestational age (SGA). Twenty-two among 154 infants that were born with low weight were preterm, and fifty-two were LBW-term SGA. The preterm low birth weight group (n = 92) had significantly lower mean Vitamin A levels than the normal birth weight group and the LBW-term SGA subgroups. However, there was no discernible difference in the mean Vitamin A values of the group born with normal birth weight and the group of babies born with low birth weight at term. It was reported that there was a significant positive link between cord blood Vitamin A level and birth weight in all of the spectrum of low birth weight newborns (n=154) ($r=0.37$, $P<0.0001$). They discovered that the preterm low birth weight kids had significantly

reduced Vitamin A levels in their cord blood. It is possible that a state of Vitamin A deficiency could have a causal link with newborn morbidity. There is sufficient data suggesting this possibility. Supplementing a newborn with Vitamin A during a vital period of their life may prove to be advantageous in the long run, even if the intervention is quite straightforward. [35]

A study was carried out by Feungpean B and colleagues in 2002 with the purpose of determining the changes in plasma Vitamin A levels that occurred over the course of first thirty days in 19 premature neonates with a very low birth weight but healthy. The subjects were given nutritional supplements consisting of multivitamins and preterm baby formula. At seven, fourteen, and thirty days age, plasma Vitamin A levels measured. At 7, 14, and 30 days of life, the amounts of Vitamin A were 24.63 micrograms per deciliter, 30.97 micrograms per deciliter, and 30.68 micrograms per deciliter, respectively. Upon observation, it was found that the Vitamin A level was considerably lower at the age of seven days compared to the levels observed at the ages of fourteen and thirty days ($p < 10\%$). At the age of seven days, three babies, belonging to the group of 19 patients, exhibited low plasma Vitamin A levels (< 20 microg/decilitre). When the newborns were fourteen and thirty days old, their Vitamin A levels were all within the usual range. According to the findings, healthy premature infants who were at risk of developing a subclinical Vitamin A deficiency in initial seven days may be successfully addressed if they received enough enteral feeding and routine multivitamin supplementation. [36]

Tammela O et al. (1999) conducted a study wherein they examined the amounts of plasma Vitamin A in cord blood samples (fifty six babies) who were delivered with gestation < 33 weeks. The outcome was monitored in a prospective manner. The utilisation of a questionnaire was utilised in order to assess the dietary

patterns of mothers as well as their utilisation of multivitamins throughout their pregnancies. Twenty-two individuals had Vitamin A levels that were below 1.05 micromol/l, which is considered to be low. However, only two of the subjects had concentrations that were below 0.7 micromol/litre, which is considered to be deficient. However, no correlation found between the Vitamin A levels with the gestation ages of the newborns. When compared to newborns with normal levels, those with low concentrations were found to have a much higher incidence of multiplets. Furthermore, the levels of Vitamin A in the multiplets were found to be significantly lower than those in the singleton pregnancies. When comparing subjects with different Vitamin A levels, the outcome measures that were utilised, as well as the mothers' diet habits ,intake of multivitamins, were also comparable. Due to the fact that there was association of low Vitamin A levels with multiple gestation pregnancies, it is probable that a comprehensive Vitamin A status evaluation should be performed in order to identify any potential deficiencies.[7]

Mean plasma retinol levels and carotene was found to be 30.3 mcg% and 43.6 mcg%, respectively, in a study conducted by Ibrahim K et al. (1991) of 200 pregnant women who were at term. There were 64 % of women Vitamin A levels that were below the normal range (less than 33 mcg%), and twenty-six percent of them had carotene levels that were inadequate or low. These mean plasma Vitamin A levels and carotene measured in the cord blood was found to be 13.8 microgram% and 16.4 microgram%. These values were found to be lower than those seen in the maternal blood at term. It was noticed that women who consumed a much larger amount of Vitamin A had more than thirty three microgram% of Vitamin A levels, which is considered to be acceptable levels. Likewise, it was noted that the newborns of moms with acceptable levels of Vitamin A had higher amounts of Vitamin A.[37]

MATERIALS AND METHODS

STUDY DESIGN:

Prospective cohort study

STUDY PERIOD:

One year (March 2023 to March 2024)

SOURCE OF DATA:

All preterm neonates <37 weeks delivered at KLES Dr. Prabhakar Kore Hospital and Medical Research centre, Belagavi.

INCLUSION CRITERIA-

Preterm neonates delivered in KLES Dr. Prabhakar Kore Hospital and Medical Research centre, Belagavi.

EXCLUSION CRITERIA-

Infants with major congenital anomalies, chromosomal anomalies and those who refused to give consent were excluded.

SAMPLESIZE

Sample size calculated using this formula,

$$n = \frac{p\,(100-p)Z^2}{E^2}$$

n == sample size

E == percentage of maximum error to be accounted

Z == number corresponding to level of confidence

P == the percentage occurrence of a state(prevalcnce-37.5%)

According to study conducted by Tao et al, “When it comes to late preterm infants, the prevalence of low umbilical cord blood Vitamin A levels below 0.7 micromol per litre was shown to be 37.5%.” Considering confidence level of 95% and a maximum error of 10%, the sample size may be calculated as :

$$n = \frac{37.5x\,(100-37.5)\,x\,1.96^2}{10^2}$$

$$n = 90.0375 \approx 90$$

Minimum sample size required ==90.

METHODOLOGY:

All neonates who were born in the labour room of KLES Dr. Prabhakar Kore hospital and who were born within the 37-week period of gestation were taken in the study. Written consent taken from the parents of newborns who fulfilled the inclusion criteria after the researchers had explained the purpose of the study to them. All of the

information on the neonate, included the gestational age, gender, birth weight, data of resuscitation, and APGAR scores, was recorded into a structured proforma.

SYSTEM USED: HUMAN VITAMIN A GENLISA™ ELISA

TEST PRINCIPLE:

The GENLISA™ ELISA kits are used for assessing the specific biomarker in samples analytes which may be serum, plasma and cell culture supernatant as validated with the kit. The kit employs a sandwich ELISA technique which leads to a higher specificity and increased sensitivity compared to conventional competitive ELISA kits which employ only one antibody. Double antibodies are used in this kit.

Principle: The method employs sandwich ELISA technique. Human Vitamin A monoclonal antibodies are pre-coated onto microwells. Samples and standards are pipetted into microwells and Human Vitamin A (VA) present in the sample are bound by the antibodies. Biotin labeled VA antibody is added and followed by Streptavidin-HRP is pipetted and incubated to form a complex. After washing microwells in order to remove any non-specific binding, substrate solution (TMB) is added to microwells and color develops proportionally to the amount of Human Vitamin A (VA) in the sample. Vitamin A levels were measured in ng/ml and converted to µmol/litre. Color development is then stopped by addition of stop solution. Absorbance is measured at 450 nm.

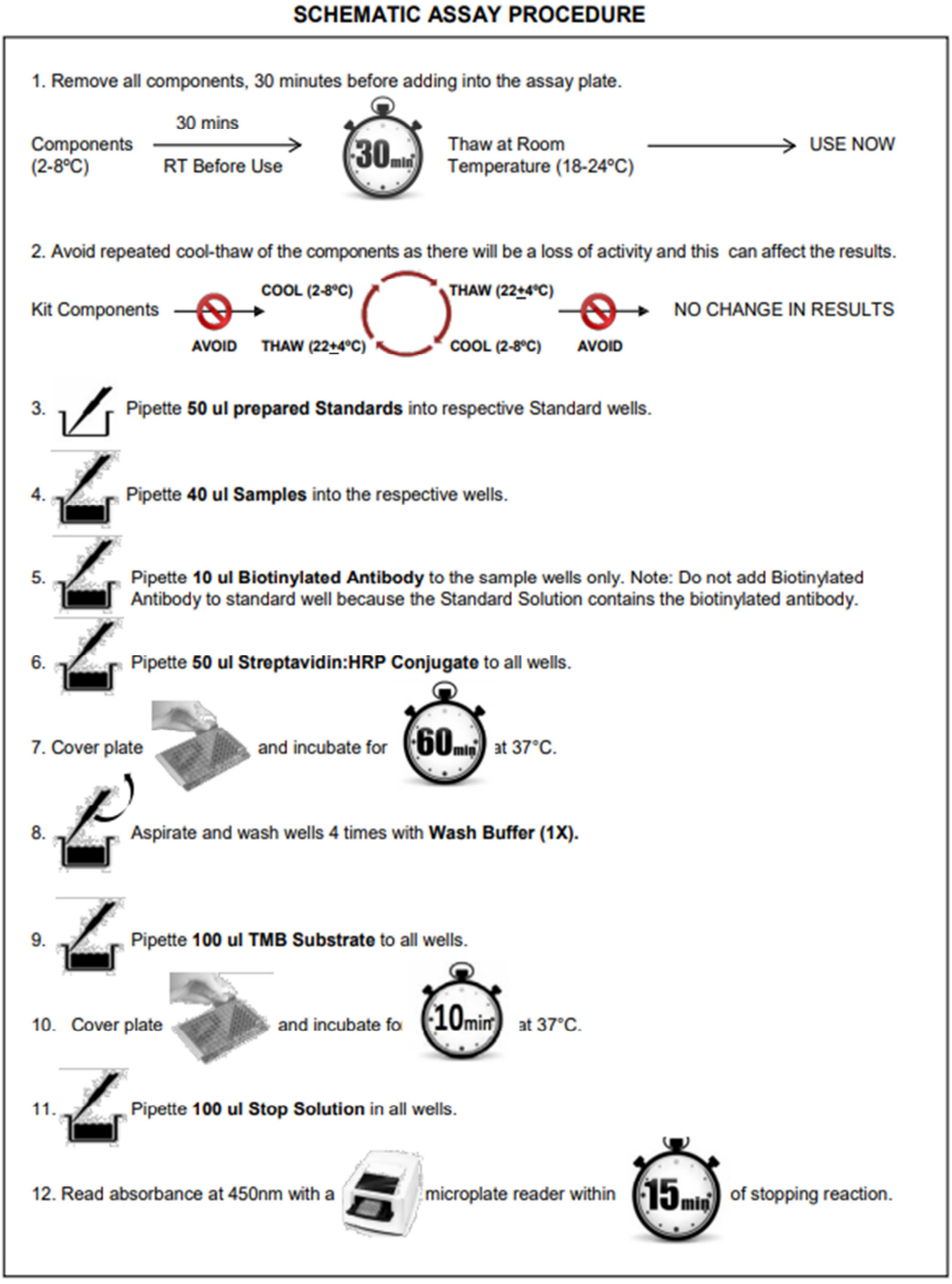


Figure 3: Schematic representation of Vitamin A ELISA Test procedure

Specimen collection: Upon delivery, about 2ml of umbilical cord blood was collected in a yellow topped sampling tube for the assessment of Vitamin A. Coagulated at room temperature- ten to twenty mins; further after centrifuging- twenty minutes at 2000to3000 rpm, samples stored at minus 20 degrees. After discarding haemolysed samples, clear, non haemolysed samples were run as early as possible at the KLE'S Basic Science Research Center. Initially 104 samples were taken and 14 samples were discarded because they were hemolysed.

Other recorded parameters for analysis: The neonates included in the study were followed up till 7 days of life that is early neonatal period and these parameters were recorded:

- At the time of admission, Clinical grading of Respiratory distress in the preterm neonates was done by Modified Downe scoring system. Diagnosis of Respiratory distress syndrome was done by Clinical and Chest X ray findings.

- All neonates with respiratory distress will be followed up for the requirement of Surfactant administration, mode of respiratory support required like Mechanical Ventilation, CPAP, oxygen supplementation through Nasal prongs and its duration respectively.

- Hyperbilirubinemia that is bilirubin levels requiring phototherapy was recorded

- Presence of Sepsis based on blood culture growth was recorded.

Table 1: Vitamin A cut offs proposed for Vitamin A normal levels, deficiency and severe deficiency:[16,37]

Normal	>0.7 micromol/Litre
Deficiency	>0.35 till < 0.7 micromol/Litre
Severe deficiency	<0.35 micromol/Litre

ANALYSIS OF STATISTICS:

In the case of quantitative variables, analysis was done using the mean and standard deviation, while frequencies and proportions were utilised for categorical variables. Additionally, relevant diagrams such as bar graphs, pie diagrams, and box plots were utilised in order to properly depict the data. By using cross tabulation and comparing percentages, we were able to gain an understanding of the relationship that exists between the variables that explain categorical outcomes. The statistical significance was determined by Chi-square test.

For normally distributed data (parametric data), The association between categorical explanatory variables and quantitative outcome was assessed by comparing the mean values. The mean differences along with presented. ANOVA (>2 groups) to assess statistical significance.

P value equal to or lesser than 0.05 was considered statistically significant. IBM SPSS version 22 was used for statistical analysis.

RESULTS

Table 2:Distribution of gender in our samples (n=90)

Sex	Frequencies	Percentages
Males	50	55.56%
Females	40	44.44%

The study sample consisted of 90 participants, with 50 males (55.56%) and 40 females (44.44%).

Table 3: Distribution according to birth weight (n=90)

Weight	Frequency	Percentages
<2 kg	58	64.44%
≥2 kg	32	35.56%

Figure 4: Piechart showing gestational ages in the study population (weeks) (N=90)

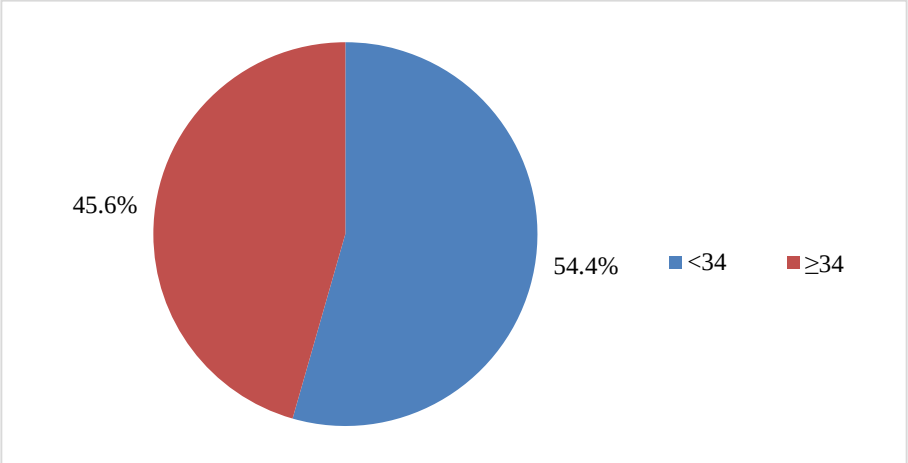


Table 4: Modes of delivery in the group (n=90)

Mode Of Delivery	Frequency	Percentage
Cesarean section	56	62.22%
Vaginal delivery	34	37.78%

Figure 5: Pie chart of oxygen need for >24hrs in the study population (N=90)

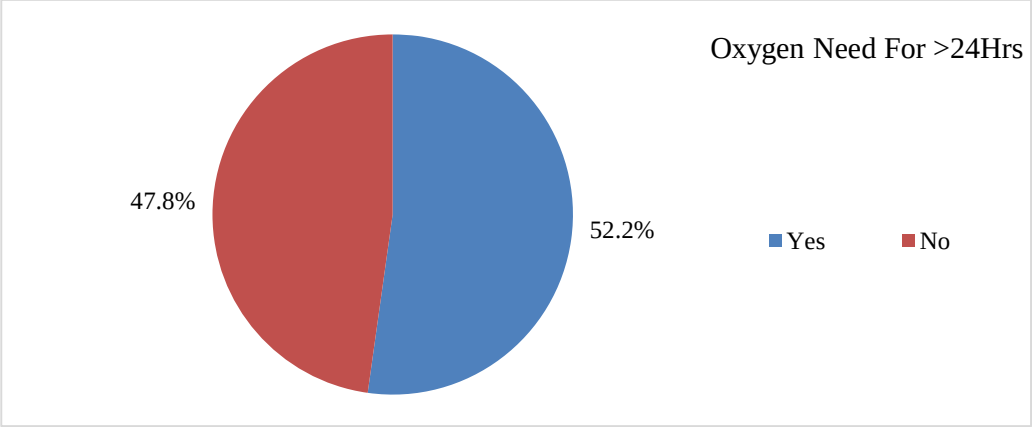


Figure :6 Pie chart of CPAP requirement in the study population (N=90)

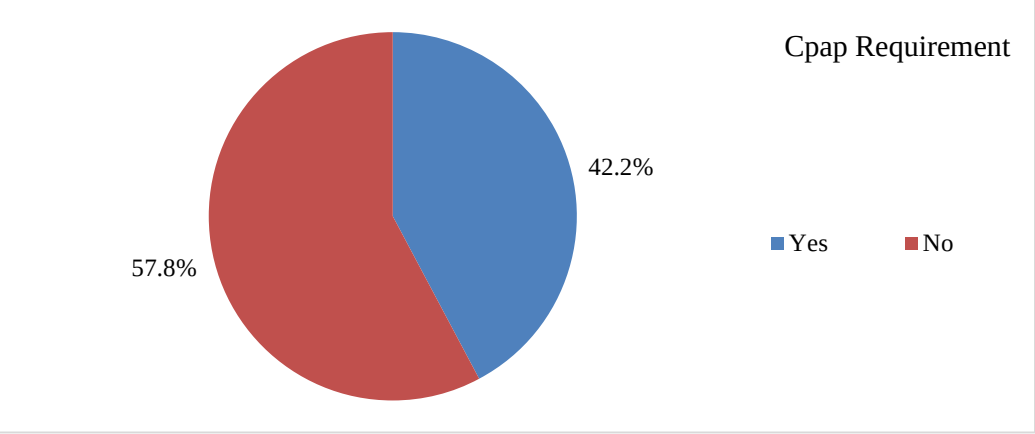


Table 5:Ventilator requirement in study sample(n=90)

Ventilator Requirement	Frequency	Percentages
Yes	12	13.33%
No	78	86.66%

Table 6:CPAP(no of days) and ventilator(no of days) in samples(n=90)

Parameter	Frequency	Percentages
CPAP (No. of Days)		
0	52	57.78%
1	14	15.56%
2	19	21.11%
3	4	4.44%
4	1	1.11%
Ventilator (No. of Days)		
0	78	86.67%
1	3	3.33%
2	3	3.33%
3	3	3.33%
4	1	1.11%
5	2	2.22%

Figure 7: Bar chart of CPAP (no of days) in the study population

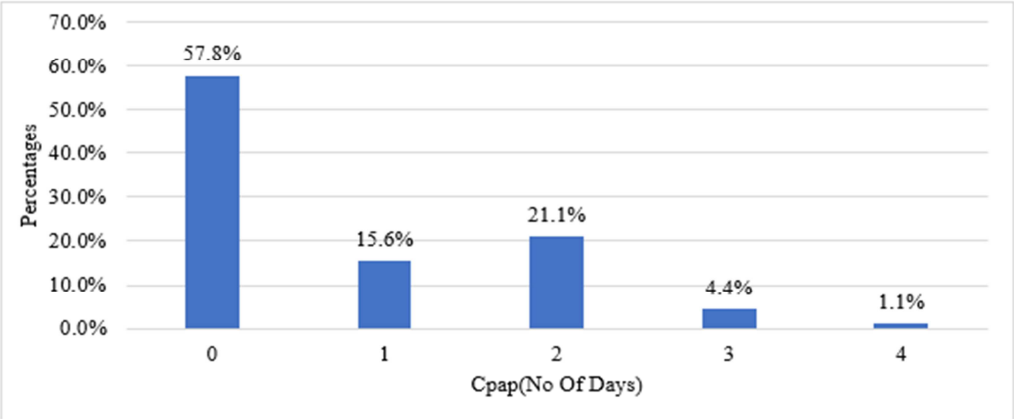


Figure 8: Bar chart of ventilator(no of days) in the study population (N=90)

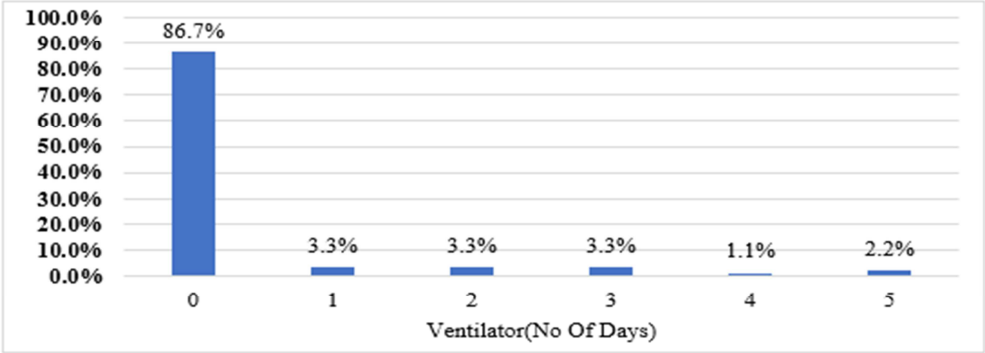
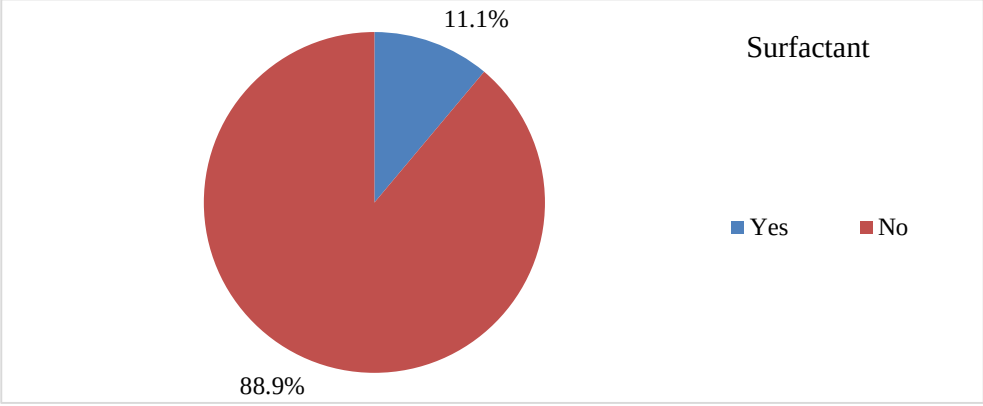


Figure 9: Pie chart of surfactant in the study population (N=90)



X-Ray	Frequency	Percentages
HMD1	5	5.56%
HMD2	5	5.56%
HMD3	10	11.11%
Normal	70	77.78%

Figure 10: Bar chart of X-Ray findings in the study population (N=90)

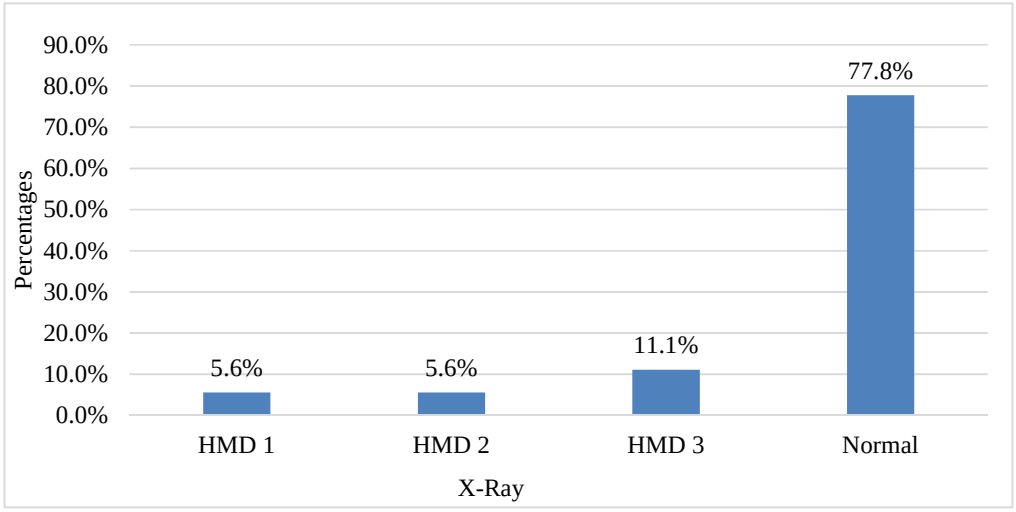


Figure 11: Pie chart of RDS in the study population (N=90)

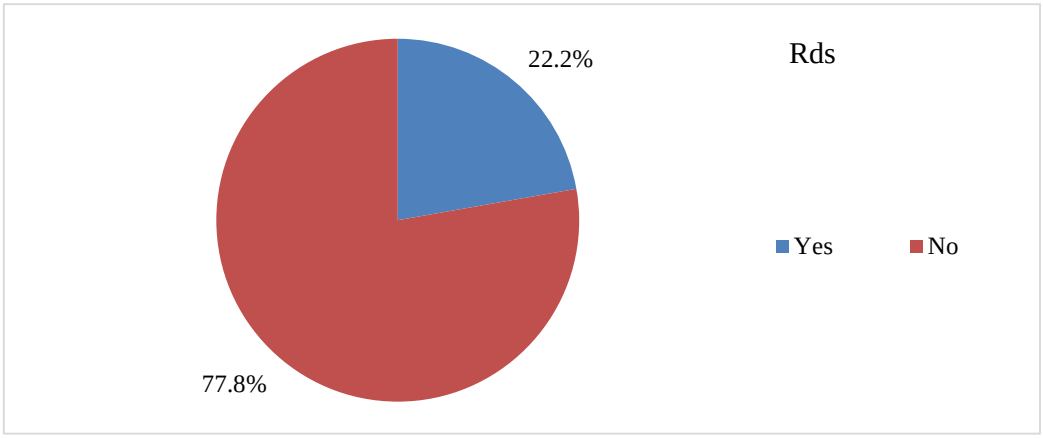


Table 7: Hyperbilirubinemia in study samples (N=90)

Hyperbilirubinemia	Frequency	Percentages
Yes	38	42.22%
No	52	57.78%

Figure 12: Pie chart of Sepsis in the study population (N=90)

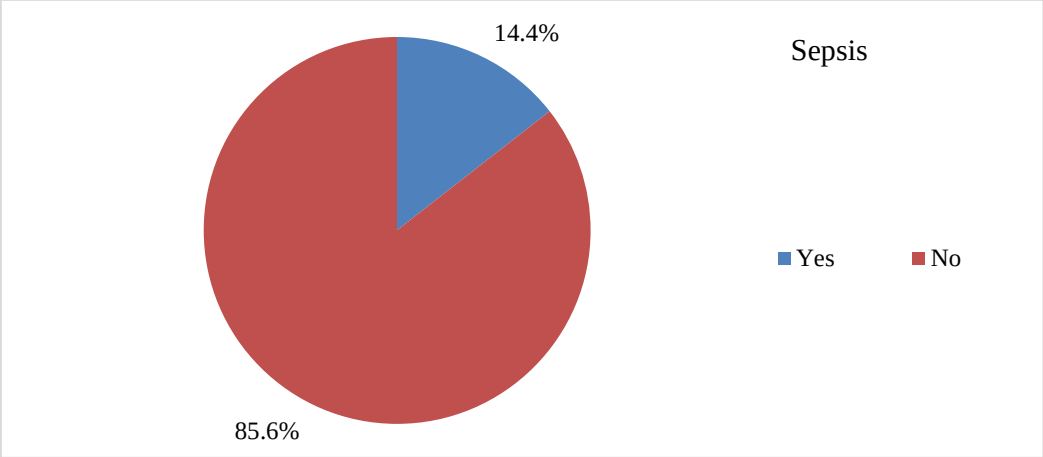
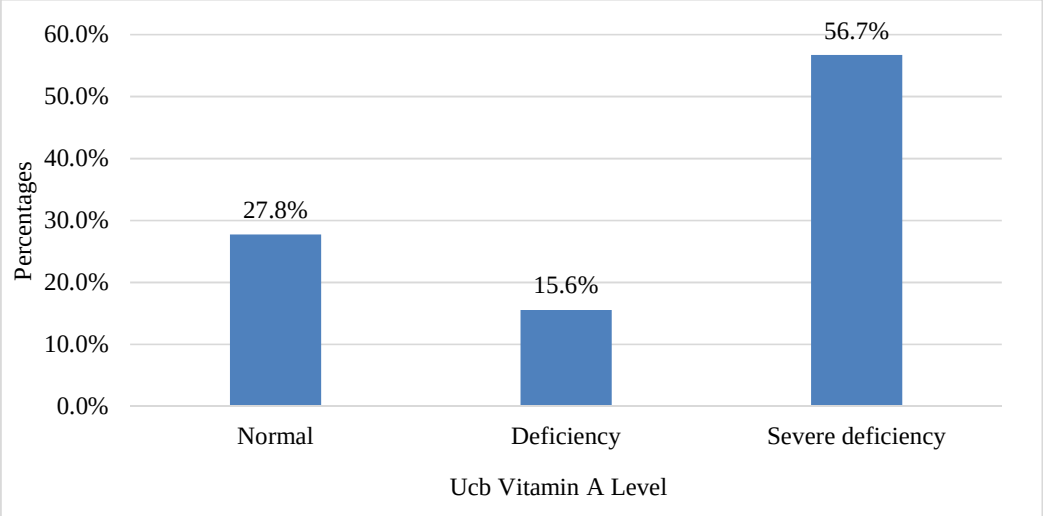


Figure 13: Bar chart of UCB Vitamin A Level in the study population (N=90)



If divided into 2 categories UCB Vitamin A level in the samples (N=90):

UCB Vitamin A Level	Frequency	Percentages
Normal	25	27.78%
Low	65	72.22%

Table 8: Comparison of mean birth weight (kg) across UCB Vitamin A level (N=90)

Parameter	UCB Vitamin A level			P Value
	Normal (N=25)	Deficiency (N=14)	Severe Deficiency (N=51)	
Birth Weight (kilograms)	1.89 ± 0.51	1.8 ± 0.52	1.77 ± 0.55	0.668

Table 9: Comparison of mean Gestational Age (Weeks) across UCB Vitamin A level (N=90)

Parameter	UCB Vitamin A level			P Value
	Normal (N=25)	Deficiency (N=14)	Severe Deficiency (N=51)	
Gestational Age	33.35 ± 2	33.47 ± 1.55	32.93 ± 2.08	0.539

Table 10: Comparison of gender across UCB Vitamin A level (N=90)

Gender	UCB Vitamin A Level			Chi square	P value
	Normal (N=25)	Deficiency (N=14)	Severe Deficiency (N=51)		
Male	12 (48%)	7 (50%)	31 (60.78%)	1.318	0.517
Female	13 (52%)	7 (50%)	20 (39.22%)		

Table 11:Comparison of mode of delivry across UCB Vitamin A level (N=90)

Mode Of Delivery	UCB Vitamin A Level			Chi square	P value
	Normal (N=25)	Deficiency (N=14)	Severe Deficiency (N=51)		
LSCS	4 (16%)	11 (78.57%)	41 (80.39%)	31.478	<0.001
NVD	21 (84%)	3 (21.43%)	10 (19.61%)		

Figure 14: Cluster bar chart of comparison of mode of delivery across UCB Vitamin A level (N=90)

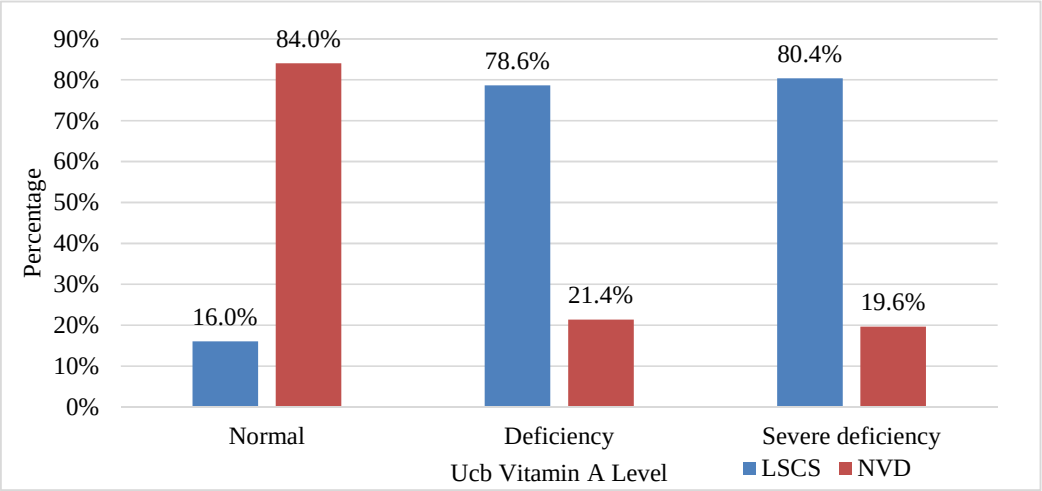


Table 12: Comparison of mean APGAR scores across UCB Vitamin A level (N=90)

Parameter	UCB Vitamin A Level			P Value
	Normal (N=25)	Deficiency (N=14)	Severe Deficiency (N=51)	
Apgar At 1 Min	6.72 ± 0.61	6.21 ± 1.63	6.57 ± 1.2	0.423
Apgar At 5 Mins	8.68 ± 0.56	8.5 ± 0.85	8.43 ± 0.78	0.390

Table 13: Comparison of oxygen need for >24hrs across UCB Vitamin A level (N=90)

Oxygen Need For >24Hrs	UCB Vitamin A Level			Chi square	P value
	Normal (N=25)	Deficiency (N=14)	Severe Deficiency (N=51)		
Yes	4 (16%)	8 (57.14%)	35 (68.63%)	18.783	<0.001
No	21 (84%)	6 (42.86%)	16 (31.37%)		

Table 14: Comparison of CPAP requirement across UCB Vitamin A level (N=90)

CPAP Requirement	UCB Vitamin A Level			Chi square	P value
	Normal (N=25)	Deficiency (N=14)	Severe Deficiency (N=51)		
Yes	0 (0%)	6 (42.86%)	32 (62.75%)	27.08	<0.001
No	25 (100%)	8 (57.14%)	19 (37.25%)		

Table 15: Comparison of ventilator requirement across UCB Vitamin A level (N=90)

Ventilator Requirement	UCB Vitamin A Level			Chi square	P value
	Normal (N=25)	Deficiency (N=14)	Severe Deficiency (N=51)		
Yes	0 (0%)	3 (21.43%)	9 (17.65%)	5.46	0.065
No	25 (100%)	11 (78.57%)	42 (82.35%)		

Figure 15: Cluster bar chart of comparison of ventilator requirement across UCB Vitamin A level (N=90)

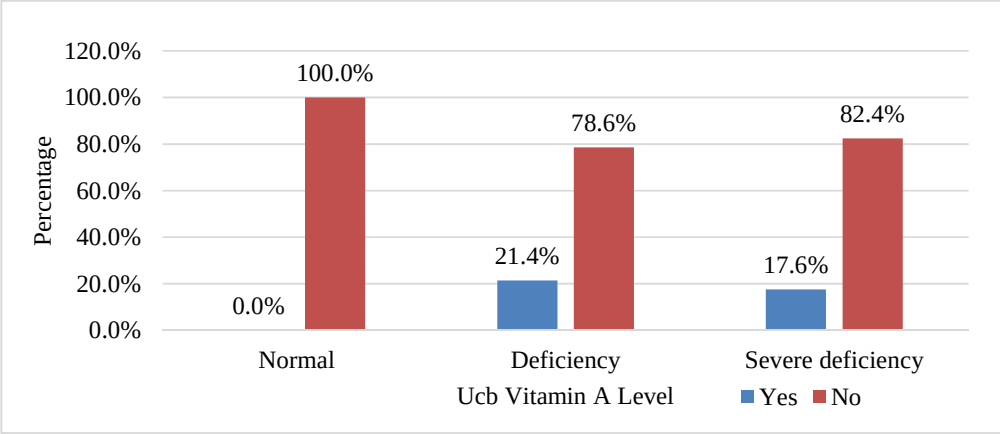


Table 16:Comparison of mean CPAP and Ventilator (No of Days across) UCB Vitamin A level (N=90)

Parameter	UCB Vitamin A level			P Value
	Normal (N=25)	Deficiency (N=14)	Severe Deficiency (N=51)	
CPAP (No of Days)	0 ± 0	0.64 ± 0.93	1.16 ± 1.07	<0.001
Ventilator (No of Days)	0 ± 0	0.71 ± 1.44	0.43 ± 1.14	0.088

Table 17: Comparison of CPAP (no of days) Across UCB Vitamin A level (N=90)

Parameter	UCB Vitamin A Level			Chi square	P value
	Normal (N=25)	Deficiency (N=14)	Severe Deficiency (N=51)		
CPAP (No of Days)					
0	25 (100%)	8 (57.14%)	19 (37.25%)	31.16	<0.001
1	0 (0%)	4 (28.57%)	10 (19.61%)		
2	0 (0%)	1 (7.14%)	18 (35.29%)		
3	0 (0%)	1 (7.14%)	3 (5.88%)		
4	0 (0%)	0 (0%)	1 (1.96%)		
Ventilator(No of Days)					
0	25 (100%)	11 (78.57%)	42 (82.35%)	18.43	0.048
1	0 (0%)	0 (0%)	3 (5.88%)		
2	0 (0%)	0 (0%)	3 (5.88%)		
3	0 (0%)	2 (14.29%)	1 (1.96%)		
4	0 (0%)	1 (7.14%)	0 (0%)		
5	0 (0%)	0 (0%)	2 (3.92%)		

Figure 16: Cluster bar chart of comparison of CPAP(no of days) across UCB Vitamin A level (N=90)

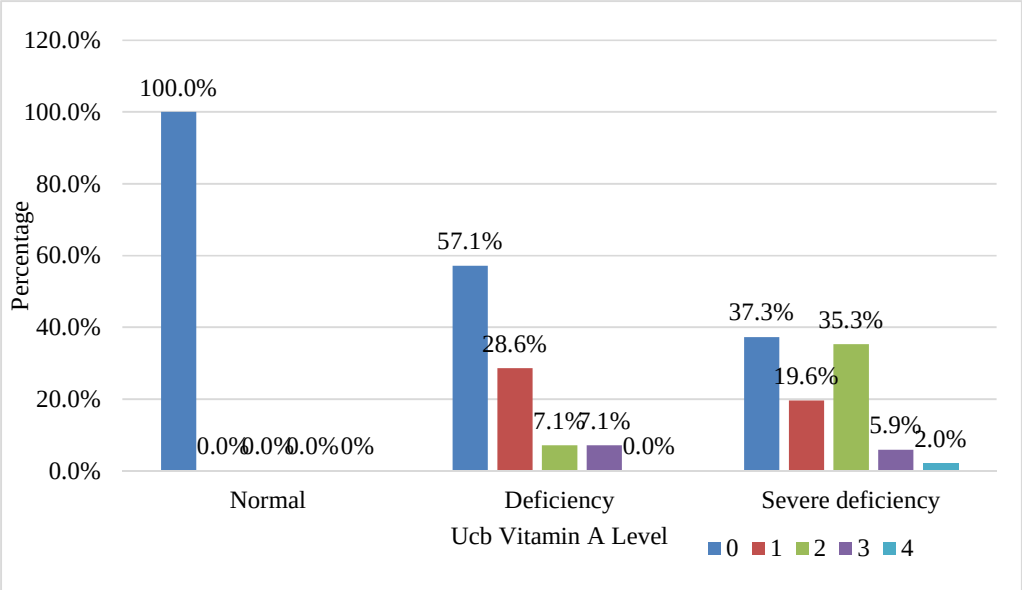


Figure 17: Cluster bar chart of comparison of ventilator(no of days) across UCB Vitamin A level (N=90)

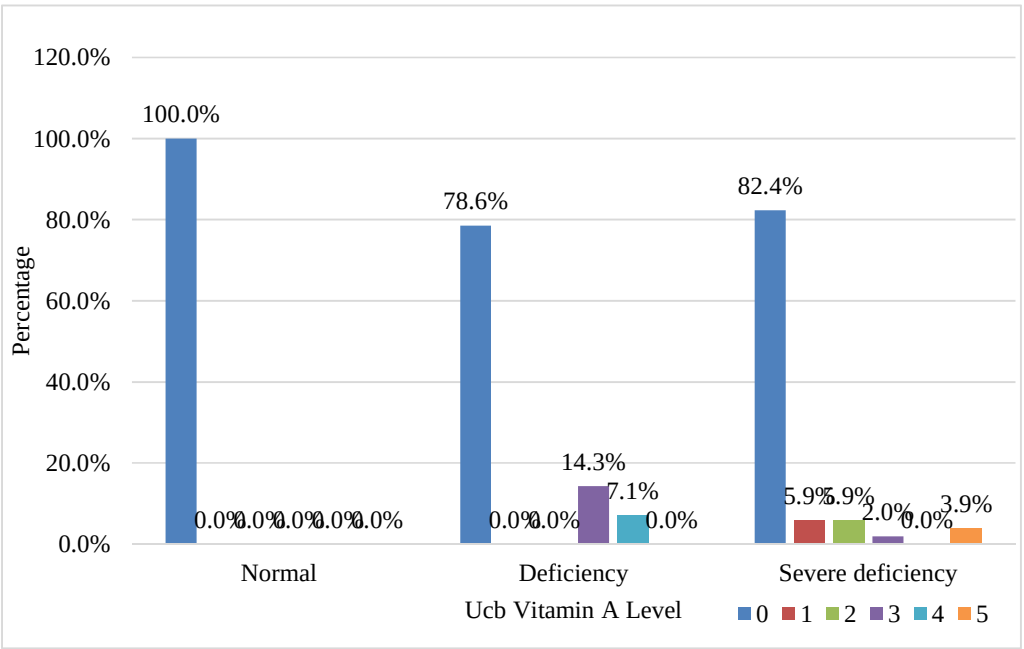
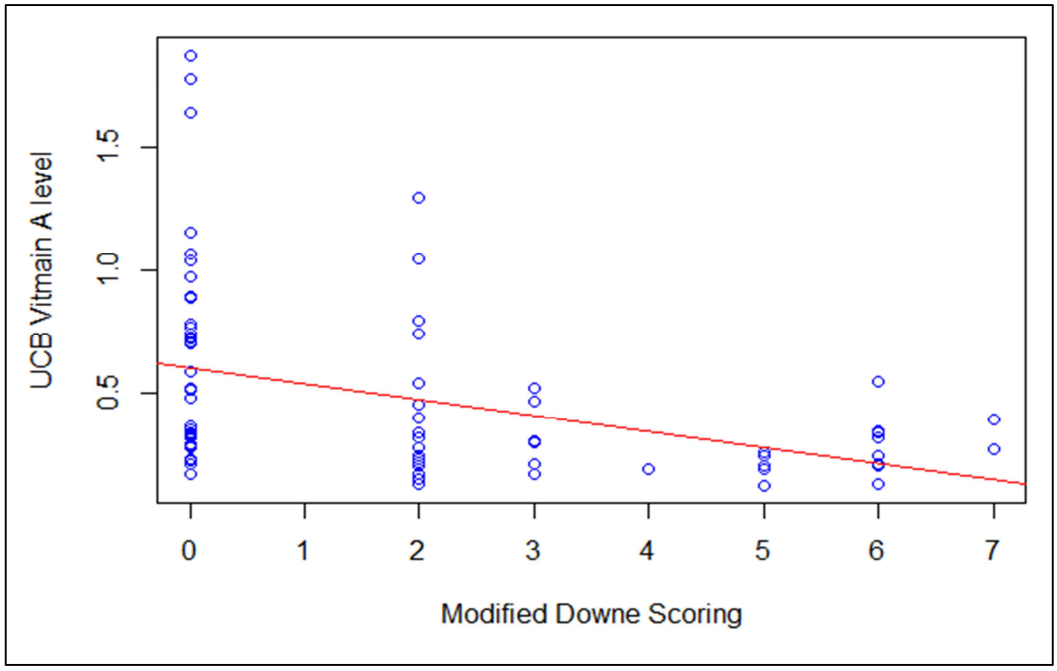


Table 18: Comparison of mean Modified Downe Scoring across UCB Vitamin A level (N=90)

Parameter	UCB Vitamin A level			P Value
	Normal (N=25)	Deficiency (N=14)	Severe Deficiency (N=51)	
Modified Downe Scoring	0.32 ± 0.75	2.21 ± 2.52	2.55 ± 2.34	<0.001



"Figure 18: Scatter plot of Modified Downe scores with UCB Vitamin A levels"

The Modified Downe Scoring has a moderate negative correlation with UCB Vitamin A levels (r == -0.4553), and this correlation is statistically significant (p value < 0.001). This shows that higher Modified Downe Scores are significantly associated with lower levels of Vitamin A.

Table 19: Comparison of surfactant across UCB Vitamin A level (N=90)

Surfactant	UCB Vitamin A Level			Chi square	P value
	Normal (N=25)	Deficiency (N=14)	Severe Deficiency (N=51)		
Yes	0 (0%)	2 (14.29%)	8 (15.69%)	4.35	0.114
No	25 (100%)	12 (85.71%)	43 (84.31%)		

Table 20: Comparison of surfactant between UCB Vitamin A level (N=90)

Surfactant	UCB Vitamin A Level		Chisquare	Pvalue
	Normal (n-25)	Low (n-65)		
Yes	0 (0%)	l0 (15.38%)	3.327	0.038
N0	25 (100%)	55 (84.62%)		

Table 21: Comparison of X-Ray across UCB Vitamin A level (N=90)

X-Ray	UCB Vitamin A Level			Chi square	P value
	Normal (N=25)	Deficiency (N=14)	Severe Deficiency (N=51)		
HMD 1	0 (0%)	0 (0%)	5 (9.8%)	12.02	0.062
HMD 2	0 (0%)	1 (7.14%)	4 (7.84%)		
HMD 3	0 (0%)	2 (14.29%)	8 (15.69%)		
Normal	25 (100%)	11 (78.57%)	34 (66.67%)		

Figure 19: Cluster bar chart of comparison of X-Ray across UCB Vitamin A level (N=90)

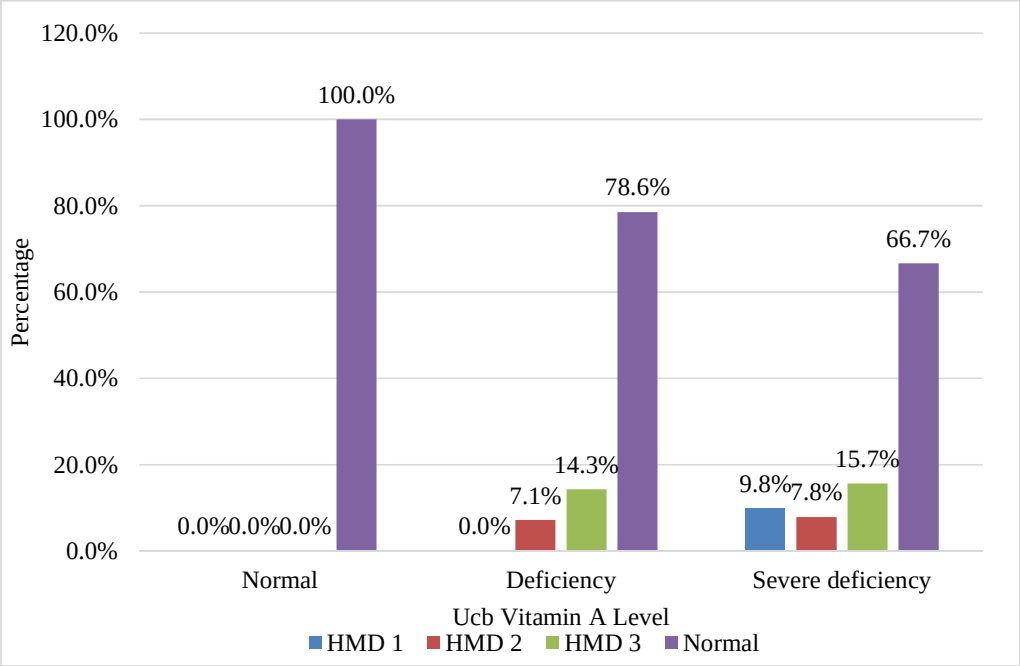


Table 22: Comparison of X-Ray between Low and normal UCB Vitamin A level groups (N=90)

X-Ray	UCB Vitamin A Level		Chi square	P value
	Normal (N=25)	Low (N=65)		
HMD 1	0 (0%)	5 (7.69%)	9.890	0.020
HMD 2	0 (0%)	5 (7.69%)		
HMD 3	0 (0%)	10 (15.38%)		
Normal	25 (100%)	45 (69.23%)		

Figure 20: Cluster bar chart of comparison of X-Ray between UCB Vitamin A level (N=90)

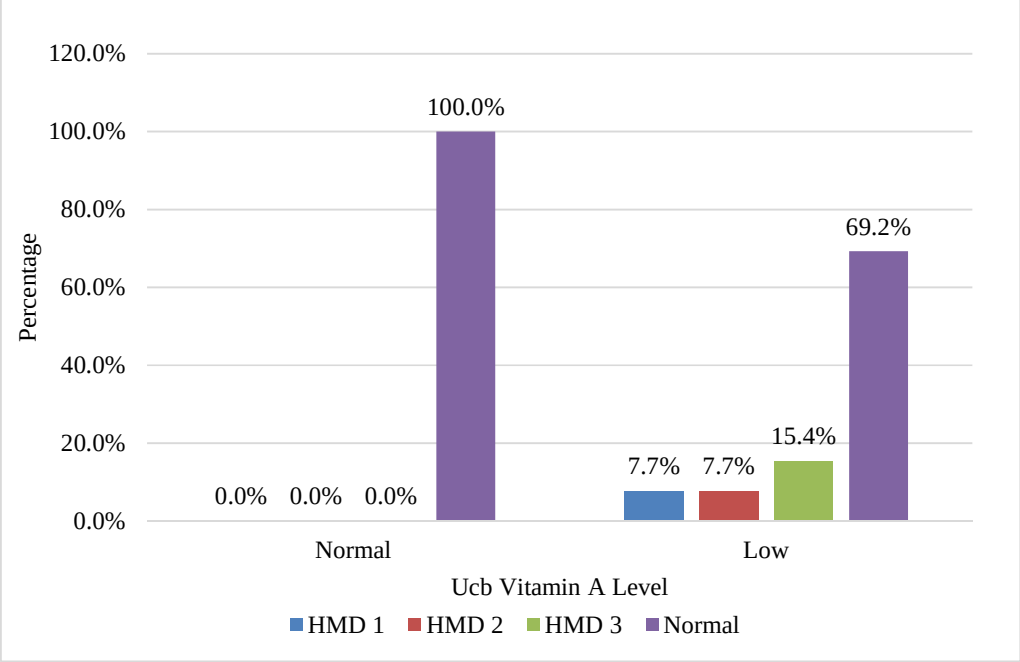


Table 23: Comparison of RDS across UCB Vitamin A level (N=90)

RDS	UCB Vitamin A Level			Chi square	P value
	Normal (N=25)	Deficiency (N=14)	Severe Deficiency (N=51)		
Yes	0 (0%)	3 (21.43%)	17 (33.33%)	10.79	0.005
No	25 (100%)	11 (78.57%)	34 (66.67%)		

Figure 21: Cluster bar chart of comparison of RDS across UCB Vitamin A level (N=90)

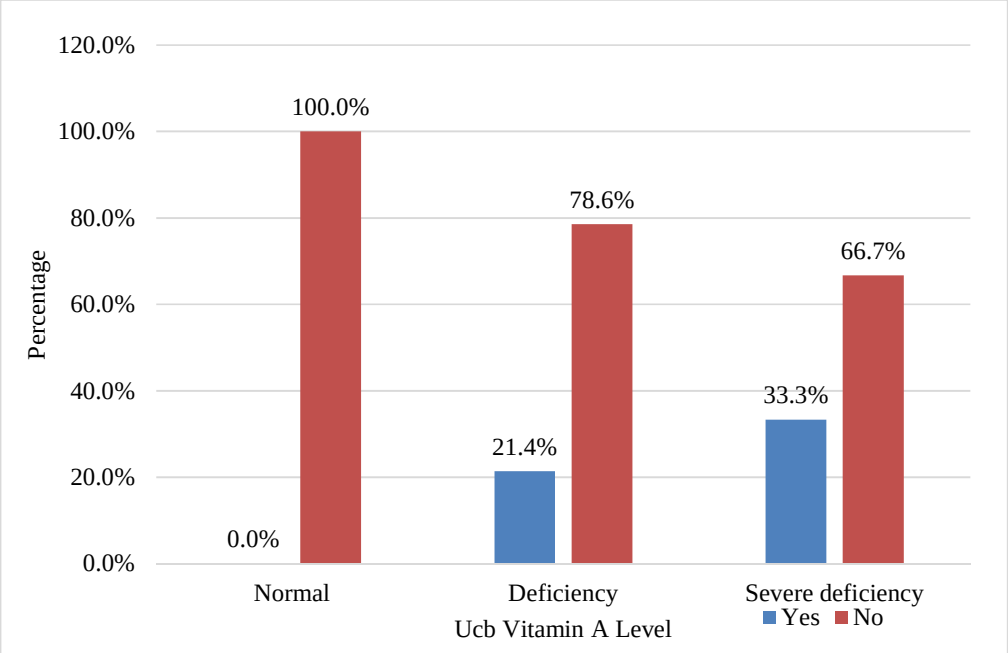


Table 24: Comparison of RDS between Normal and Low UCB Vitamin A level groups (N=90)

RDS	UCB Vitamin A Level		Chi square	P value
	Normal (25babies)	**Low (65babies)**		
Yes	0 (0%)	20 (30.77%)	9.890	0.002
No	25 (100%)	45 (69.23%)		

Table 25: Comparison of Hyperbilirubinemia across UCB Vitamin A level (N=90)

Hyperbilirubinemia	UCB Vitamin A Level			Chi square	P value
	Normal (N=25)	Deficiency (N=14)	Severe Deficiency (N=51)		
Yes	5 (20%)	6 (42.86%)	27 (52.94%)	7.465	0.024
No	20 (80%)	8 (57.14%)	24 (47.06%)		

Figure 22: Cluster bar chart of comparison of Hyperbilirubinemia across UCB Vitamin A level (N=90)

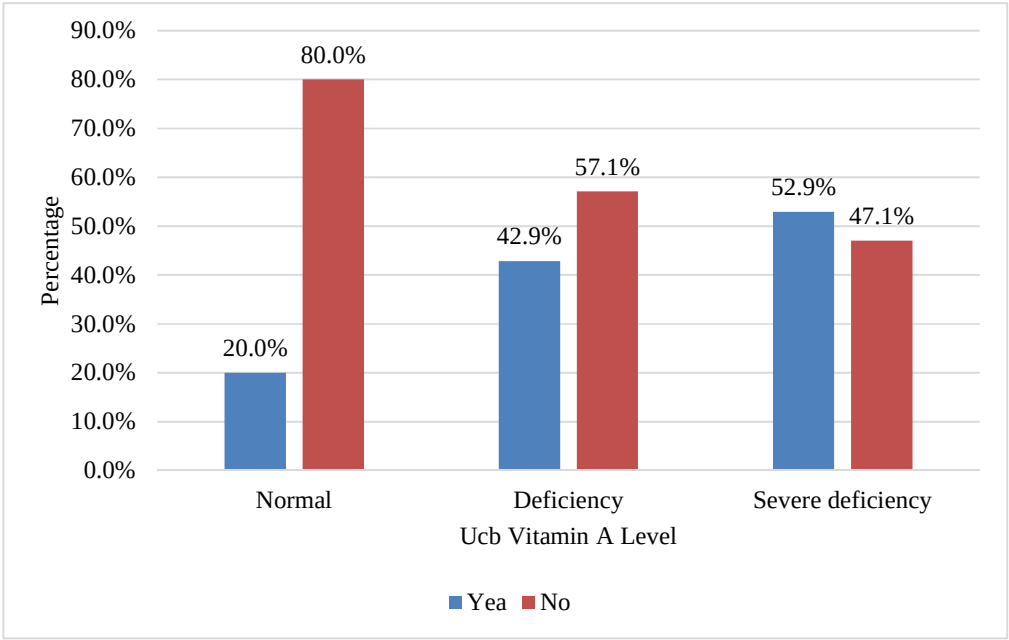


Table 26: Comparison of sepsis across UCB Vitamin A level (N=90)

Sepsis	UCB Vitamin A Level			Chi square	P value
	Normal (N=25)	Deficiency (N=14)	Severe Deficiency (N=51)		
Yes	1 (4%)	1 (7.14%)	11 (21.57%)	4.905	0.086
No	24 (96%)	13 (92.86%)	40 (78.43%)		

Figure 23: Cluster bar chart of comparison of sepsis across UCB Vitamin A level (N=90)

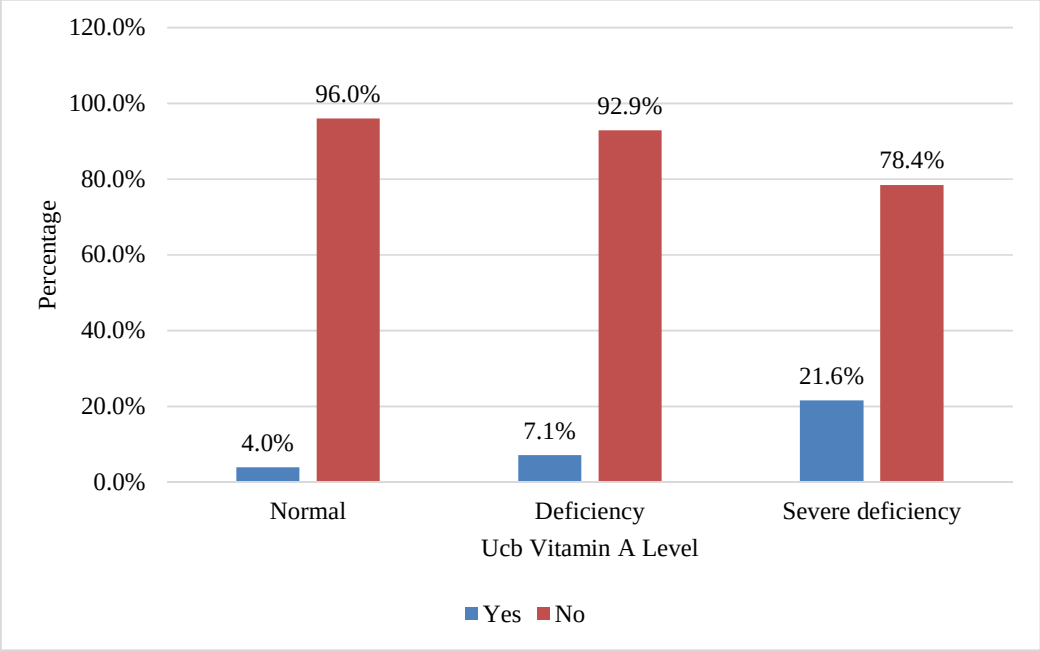


Table 27: Comparison of Sepsis between UCB Vitamin A level (N=90)

Sepsis	UCB Vitamin A Level		Chi square	P value
	Normal (25babies)	Low (65babies)		
Yes	1 (4%)	12 (18.46%)	3.056	0.102
No	24 (96%)	53 (81.54%)		

Analysis:

Among the 90 subjects, 55.56% are male and 44.44% are female. The majority (64.44%) have birth weight of lcss than 2 kg, with mcan birth weight of 1.81 ± 0.53 kilograms. Mean gestational age is 33.13 ± 1.98 weeks and median of 33.71 weeks, with 54.44% born before 34 weeks. Regarding the mode of delivery, 62.22% were delivered via LSCS, while 37.78% had a normal vaginal delivery.

APGAR scores at 1 minute ranged predominantly between 6 and 8, with a mean of 6.56 ± 1.15. At 5 minutes, most scores were 8 or 9, with a mean of 8.51 ± 0.74. Just over half the infants (52.22%) required oxygen for more than 24 hours, and 42.22% needed CPAP. A smaller portion (13.33%) required ventilator support.

The Modified Downe Scoring indicates that nearly half the subjects (48.89%) had a score of 0, but scores ranged up to 7. Only a minority received surfactant, and 22.22% were diagnosed with RDS. Hyperbilirubinemia was present in 42.22% of the subjects, and 14.44% had sepsis.

This distribution highlights a significant prevalence of Vitamin A deficiency in the subjects, with 65 individuals (72.22%) having low Vitamin A levels. Regarding Vitamin A levels, 56.67% of the subjects exhibited severe deficiency, 15.56% had a deficiency, and only 27.78% had normal levels.

Gender does not significantly impact Vitamin A levels (p-value = 0.517) nor does birth weight (p-value = 0.668), although lower birth weights tend to have higher rates of deficiency. Gestational age also shows no significant difference (p-value = 0.54), with all Vitamin A levels having similar distributions. Mode of delivery is significantly associated with Vitamin A levels (p-value < 0.001), as a higher proportion of severe deficiency cases were delivered by LSCS (80.39%).

APGAR scores at 1 and 5 minutes don't show significant differences across Vitamin A levels (p value = 0.423 and p value = 0.390, respectively). However, oxygen needs for more than 24 hours and CPAP requirements (p value < 0.001) are significantly associated with severe Vitamin A deficiency, with more deficient infants requiring these interventions. Ventilator requirements are not significantly different (p-value = 0.06), but the number of days on a ventilator is (p-value = 0.048), with severe deficiency cases requiring more days.

Modified Downe Scoring is significantly higher in severely deficient infants (p-value < 0.001).

The Modified Downe Scoring has a moderate negative correlation with UCB Vitamin A levels , and this correlation is statisticaly significant (p value < 0.001). This suggests higher Modified Downe Scores are significantly associated with lower levels of UCB Vitamin A.

Chest X-ray results indicate a non-significant trend towards higher HMD scores in severe deficiencies (p-value = 0.0580). When examining X-ray results, none of the infants with normal UCB Vitamin A levels showed signs of HMD, whereas various degrees of HMD were present in 30.76% of those with low levels. This difference reached statistical significance (p-value=0.02).

For surfactant administration, most infants with low UCB Vitamin A levels (84.62%) did not receive any doses, while all infants with normal levels did not receive any doses. However, the difference here was not statistically significant among deficiency and severe deficiency groups (p-value =0.114) but it was significant between normal and low Vitamin A groups(p=0.038)

RDS is significantly associated with Vitamin A levels (p-value = 0.005), with RDS present in 30.77% of infants with low Vitamin A levels, none in normal group: as is hyperbilirubinemia (p-value = 0.024), occurring in 50.77% of the low Vitamin A group compared to 20% of in normal group. Sepsis rates do not differ significantly across the Vitamin A levels (p-value = 0.086).

DISCUSSION

Infants and early children have higher Vitamin A requirements than adults because they are more likely to have rapid growth and to be more susceptible to illnesses. In early newborns, the Vitamin A status is affected by the amount of Vitamin A that is stored in their livers at birth, the amount of Vitamin A that is consumed via breast milk and other meals, and the amount of Vitamin A that is lost due to illness, particularly those that are caused by parasites.[45]The majority of the time, newborns born with inadequate Vitamin A stores in their livers, despite the mother having sufficient amount of Vitamin A in her body[46]. Infants in nations with low and intermediate incomes are more likely to acquire insufficient levels of Vitamin A. This is partially because of low Vitamin A concentration in breast milk, along with poor nutrition condition of mother. Vitamin A deficiency may increase illness chances and death from childhood infections like measles, those that cause diarrhoea[47]. In order to minimise infant mortality in southern Asia, a promising new intervention known as new born Vitamin A supplementation (NVAS) has been developed. This intervention includes administering a single high oral dosage of Vitamin A to infants shortly after birth. The dose is 50,000 international units (IU)[50]. "For infants less than 6 months of age, there is substantial evidence that a dose of up to 50 000 IU of Vitamin A is safe"[48]. Acute side effects are temporary and include agitation, vomiting, diarrhoea, loss of appetite, and bulging fontanelles, which is the most commonly reported adverse effect caused by this medication. With smaller hepatic reserves, preterm newborns show lower plasma concentrations of both retinol and retinol binding protein after birth. This is in comparison to term infants, who have higher plasma concentrations of both of these substances. Because of this, it is

essential to address the Vitamin A shortage that they have. The present study was conducted on preterms delivered at KLE DR. Prabhakar Kore hospital, Belagavi.

CORD BLOOD VITAMIN A LEVELS

In this study, majority of preterm infants have low Vitamin A levels, with 72.22% in low category compared to 27.78% with normal levels. Low Vitamin A levels are associated with adverse outcomes, including an increased risk of infections, impaired growth, and other morbidities during the early neonatal period. The fact that nearly three-quarters of the preterm infants have low Vitamin A levels highlights the importance of monitoring and potentially supplementing Vitamin A in these infants to improve their outcomes. Mean cord blood Vitamin A level of 0.48 µmol/L and the median of 0.33 µmol/L suggest that the majority of preterm infants in the study have Vitamin A levels on the lower end of the spectrum. The wide range of Vitamin A levels (from 0.13 to 1.87 µmol/L) indicates considerable variability among the infants.

In Tao E et al., "Median Cord Blood Vitamin A level of late preterm infants was 0.754 micromol/L (0.656, 0.892) and prevalence of low cord blood Vitamin A level < 0.7 micromol/L was 37.5% in late preterm infants." [4] In another study, according to Agarwal DK et al., "Mean Vitamin A level in 61 samples of cord blood was 62.8 ± 32.8 µg/dl as against 80.6 ± 39.6 µg/dl of mother's serum."[49]

In another study, according to Galinier et al., "Cord Blood Vitamin A level less than 1.05 µmol/L was measured in 22 of 56 and levels below 0.7 µmol/L only measured in 2 of 56 for gestational age < 33 weeks[7], results were inconsistent

,possible influence factors were different gestational age and birth weight of study participants. Nevertheless, preterm infants are prone to low Vitamin A level."[38]

Our results showed the prevalence of low Umbilical Cord blood Vitamin A levels in preterm babies to be high. Several reasons might be there for this. Fetuses cannot synthesize Vitamin A, , primarily depend on maternal placental supply in last part of pregnancy[39]. Preterm newborns cannot synthesize enough retinol binding protein to transport Vitamin A. [16,40]

GENDER

In this study, slight predominance of male infants was seen with males comprising 55.56% and females 44.44%. This gender distribution is relatively balanced but indicates a higher number of male preterm infants. Some studies suggest that male and female infants can have different nutritional requirements and health outcomes, which could potentially affect their Vitamin A status and susceptibility to morbidities. The gender distribution was analysed based on cord blood Vitamin A levels among newborns. In the normal Vitamin A level group (N=25), 12 (48%) were male and 13 (52%) were female. In the deficiency group (N=14), 7 (50%) were male and 7 (50%) were female. In the severe deficiency group (N=51), 31 (60.78%) were male and 20 (39.22%) were female. No statistically significant association between gender and cord blood Vitamin A levels was seen.

According to Tao E et al., "There was no significant difference in cord blood Vitamin A levels between males and females. Specifically, 38.4% of males and 36.5% of females had Vitamin A levels below 0.7 micromol/L, with a p-value of 0.87 indicating no significant difference." [4]

BIRTH WEIGHT

In this study, majority (64.44%) of the babies have a birth weight of less than 2 kg, while 35.56% have a birth weight of 2 kg or more. This distribution reflects the common occurrence of low birth weight among preterm infants. Low birth weight is a critical factor that can influence various health outcomes in the neonatal period. Infants with a birth weight of less than 2 kg are at higher risk for complications such as respiratory distress, infections, and nutritional deficiencies, including low Vitamin A levels. The prevalence of low birth weight in this study underscores the importance of closely monitoring these infants and providing appropriate nutritional and medical interventions to support their development and health.

The birth weights of newborns were analysed based on their umbilical cord blood Vitamin A levels. The mean birth weight was 1.89 ± 0.51 kg for those with normal Vitamin A levels (N=25), 1.8 ± 0.52 kg for those with a deficiency (N=14), and 1.77 ± 0.55 kg for those with severe deficiency (N=51). The differences in birth weights among the three groups were not statistically significant (P = 0.668).

In Tao E et al., 47.4% of infants weighing less than 2500 grams had low Vitamin A levels compared to 31.8% of those weighing 2500 grams or more. This difference was also statistically significant, with a P-value of 0.026. [4]

GESTATIONAL AGE

In this study, slight majority (54.44%) of the neonates were born at a gestational age of less than 34 weeks, while 45.56% were born at or after 34 weeks. This distribution highlights the variation in prematurity within the study population. Gestational age is an important factor crucial factor influencing neonatal health

outcomes. Infants born before 34 weeks of gestation are generally more vulnerable to complications, including respiratory distress syndrome, infections, and nutritional deficiencies like low Vitamin A levels, compared to those born at or after 34 weeks.

In this study, Mean gestational age for infants with normal Vitamin A levels (N=25) was 33.35 ± 2.00 weeks, for those with Vitamin A deficiency (N=14) it was 33.47 ± 1.55 weeks, and for those with severe Vitamin A deficiency (N=51) it was 32.93 ± 2.08 weeks. The p-value for this association was 0.539, indicating no statistically significant difference in gestational age among the groups with normal, deficient, and severely deficient Vitamin A levels.

In Tao E et al., there was a significant difference. Among preterm infants (< 35 weeks), 56.7% had Vitamin A levels below 0.7 μmol/L compared to 34.3% of full-term infants (≥ 35 weeks). This suggests that preterm infants are more likely to have lower Vitamin A levels, with a p-value of 0.02 indicating statistical significance. [4]

MODE OF DELIVERY

In this study, majority (62.22%) of preterm infants in the study were delivered by Lower Segment Cesarean Section (LSCS), while 37.78% were delivered via Normal Vaginal Delivery (NVD). This distribution suggests a higher prevalence of cesarean sections among preterm births in the study population. The mode of delivery can influence various neonatal outcomes. Cesarean sections, especially when performed before labor onset, can be associated with increased risks of respiratory complications and other morbidities in preterm infants. Additionally, the decision for cesarean delivery is often influenced by medical indications that might also affect neonatal outcomes, including low Vitamin A levels.

In this study, among infants with normal Vitamin A levels, 16% were delivered by Lower Segment Cesarean Section (LSCS) and 84% by Normal Vaginal Delivery (NVD). 78.57% of those with Vitamin A deficiency and 80.39% of those-severe Vitamin A deficiency were delivered by LSCS. High prevalcnce of Vitamin A deficiency is seen inspite of all mothers receiving pre delivery steroid doses as per hospital policy. For those with Vitamin A deficiency, only 21.43% were delivered by NVD, and 19.61% of those with severe deficiency were delivered by NVD. This highly significant p-value indicates a strong association between the mode of delivery and cord blood Vitamin A levels. Specifically, infants delivered by LSCS are significantly more likely to have Vitamin A deficiency or severe deficiency compared to those delivered by NVD. This finding suggests that the mode of delivery might be important factor influencing Vitamin A levels in preterm infants. The higher prevalence of Vitamin A deficiency and severe deficiency among infants delivered by LSCS could be due to various factors, such as differences in the timing of delivery like preterm deliveries, maternal health conditions prompting cesarean sections, or differences in the stress response and nutrient transfer during delivery.

In Tao E et al., the mode of delivery showed a significant impact on Vitamin A levels. Only 20.3% of vaginally delivered infants had low Vitamin A levels, whereas 62.4% of those delivered by cesarean section had low levels. The P-value for this category was less than 0.001, indicating a strong statistical significance. [4]

According to Gonzalez-Corbella et al.., Vaginal deliveries without anesthesia are more stressful than cesarean deliveries, and this stress can increase maternal corticosteroids which increase placental cord concentrations of Vitamin A, hence lower and higher cord blood Vitamin A levels in cesarean section and vaginal

deliveries, respectively. Contrastingly, Gonzalez Corbella et al. in their study reported no significant difference in Vitamin A levels between vaginal and cesarean deliveries[41,42].

APGAR AT 1 MIN & 5 MIN

In this study, Apgar score at 1 minute has a mean of 6.56 with a standard deviation (SD) of 1.15, a median of 7.0, and ranges from 2.0 to 8.0. The 95% confidence interval (CI) for the mean Apgar score at 1 minute is between 6.3 and 6.8. This suggests that the majority of preterm infants have Apgar scores around 6 to 7 at 1 minute, indicating varying levels of distress and the need for initial medical intervention. Apgar score at 5 minutes shows improvement, with a mean of 8.51 and an SD of 0.74, a median of 9.0, and scores ranging from 6.0 to 10.0. The 95% CI for the mean Apgar score at 5 minutes is between 8.4 and 8.7. This indicates that most preterm infants have improved Apgar scores by 5 minutes, with scores typically falling between 8 and 9, reflecting better physical condition and response to any initial interventions provided after birth. The increase in the mean Apgar score from 1 minute to 5 minutes demonstrates that many preterm infants stabilize and improve quickly after birth, likely due to medical interventions provided immediately after delivery. This improvement is a positive indicator of the neonatal care provided to these infants. Mean Apgar score at 1 minute for infants with normal Vitamin A levels was 6.72 ± 0.61, for those with Vitamin A deficiency it was 6.21 ± 1.63, and for those with severe Vitamin A deficiency it was 6.57 ± 1.20. At 5 minutes, the mean Apgar scores were 8.68 ± 0.56 for infants with normal Vitamin A levels, 8.50 ± 0.85 for those with deficiency, and 8.43 ± 0.78 for those with severe deficiency. The p-values

for the associations between cord blood Vitamin A levels and Apgar scores are 0.423 for the 1-minute Apgar score and 0.390 for the 5-minute Apgar score.

OXYGEN NEEDS FOR >24HRS

In this study, slight majority (52.22%) of preterm infants required oxygen therapy for more than 24 hours, while 47.78% did not require such extended oxygen support. The need for prolonged oxygen therapy is an important indicator of respiratory distress and other complications commonly associated with preterm birth. Preterm infants often have underdeveloped lungs and are at higher risk for conditions such as RDS, which necessitates extended oxygen support. This finding highlights the prevalence of respiratory challenges in preterm infants and underscores the necessity for adequate respiratory support and monitoring in neonatal care units.

In this study, among infants with normal Vitamin A levels, only 16% required oxygen for more than 24 hours, whereas 84% did not. 57.14% of infants with Vitamin A deficiency and 68.63% ,they required prolonged oxygen therapy. For those with Vitamin A deficiency, 42.86% did not require prolonged oxygen therapy, and 31.37% of those with severe deficiency did not need extended oxygen support. Significant p-value indicates a strong association between the need for prolonged oxygen therapy and cordblood Vitamin A levels. Specifically, infants with Vitamin A deficiency or severe deficiency are significantly more likely to require oxygen therapy for more than 24 hours compared to those with normal Vitamin A levels. This finding suggests that lower Vitamin A levels in preterm infants are associated with a higher need for prolonged respiratory support. Vitamin A is essential for lung development, immune function, and its deficiency may contribute to increased respiratory complications, necessitating extended oxygen therapy.

According to Tao E et al., "Vitamin A level < 0.7 μmol/L was not found to be an independent risk factor for hospitalization, oxygen supplementation, and RDS in late preterm infants." [4] In As per Chen HJ et al., "Retinol deficiency was significantly associated with adverse pulmonary outcomes, including long-term oxygen dependence (>90 days) and increased risk of bronchopulmonary dysplasia."[5]

Kiatchoosakun et al. suggested that Vitamin A supplementation could reduce intubation time and oxygen supplementation, while also shortening the length of hospital stay.[43] However, another study reported there was no significant difference in the duration of oxygen therapy between Vitamin A supplemented and control groups[44].

CPAP REQUIREMENT

In this study, 42.22% of preterm infants required CPAP therapy, while 57.78% did not require CPAP. CPAP therapy is often used to provide continuous airway pressure to preterm infants who have breathing difficulties, helping to keep their airways open and improve oxygenation. 42.22% of the infants in the study required CPAP suggests a significant prevalence of respiratory issues among the preterm population, although a larger proportion (57.78%) did not need this intervention.

In this study, among infants with normal Vitamin A levels, none required CPAP therapy, whereas 100% did not need it. In contrast, 42.86% of infants with Vitamin A deficiency and 62.75% of those with severe Vitamin A deficiency required CPAP therapy. For those with Vitamin A deficiency, 57.14% did not require CPAP therapy, and 37.25% of those with severe deficiency did not need CPAP support. Significant p-value indicates a strong association between the requirement for CPAP

therapy and cord blood Vitamin A levels. Specifically, infants with Vitamin A deficiency or severe deficiency are significantly more likely to require CPAP therapy compared to those with normal Vitamin A levels. This finding suggests that lower Vitamin A levels in preterms are associated with a higher need for respiratory support using CPAP therapy. Vitamin A plays a crucial role in lung development, immune function, and its deficiency may lead to increased respiratory complications, necessitating CPAP therapy.

VENTILATOR REQUIREMENT

In this study, 13.33% of preterm infants required ventilator support, while 86.67% did not need this level of respiratory assistance. Ventilator support is typically reserved for infants with severe respiratory distress or failure, where other forms of respiratory support, such as CPAP, are insufficient. The majority of preterm infants (86.67%) not requiring ventilator support indicates that many preterm infants either have adequate respiratory function or respond well to less intensive interventions. This is a positive indicator of the overall respiratory stability in most of the preterm infants in the study.

In this study, none of the infants with normal Vitamin A levels required ventilator support, 100% of them did not need it. 21.43% of infants with Vitamin A deficiency and 17.65% of those with severe Vitamin A deficiency required ventilator support. Among those with Vitamin A deficiency, 78.57% did not require ventilator support, and 82.35% of those with severe deficiency did not need it. Ventilator requirements are not significantly different(p-value=0.06) or we can say borderline significant, but the number of days on a ventilator is(p-value= 0.048), with severe deficiency requiring more days. This finding suggests that while there appears to be a

higher proportion of infants with Vitamin A deficiency or severe deficiency requiring ventilator support compared to those with normal Vitamin A levels, the difference is not statistically significant.

In Chen HJ et al., no specific mention of ventilator requirement, but retinol deficiency associated with adverse pulmonary outcomes and bronchopulmonary dysplasia.[5]

MODIFIED DOWNE SCORING

In this study, mean Modified Downe Score of 1.88 suggests that, on average, the preterm infants in the study experienced mild respiratory distress. The median score of 2.0 aligns with the mean, indicating that the central tendency of the scores is consistent with mild distress. The wide range of scores (from 0.0 to 7.0) highlights variability in the severity of respiratory distress among the infants, with some experiencing no distress and others experiencing more severe symptoms. The 95% confidence interval (1.4 to 2.4) further supports the conclusion that most infants in the study experienced mild respiratory distress, with the true mean score likely falling within this range.

In this study, mean Modified Downe Score for infants with normal Vitamin A levels is 0.32 ± 0.75, for those with Vitamin A deficiency it is 2.21 ± 2.52, and for those with severe Vitamin A deficiency it is 2.55 ± 2.34. The p-value for this association is less than 0.001, indicating a highly significant relationship between cord blood Vitamin A levels and the severity of respiratory distress. Specifically, infants with Vitamin A deficiency or severe deficiency exhibit significantly higher Modified Downe Scores, reflecting more severe respiratory distress, compared to

those with normal Vitamin A levels. This finding suggests that lower Vitamin A levels in preterm infants are strongly associated with increased respiratory distress. Given the crucial part of Vitamin A in lung development and immune function, its deficiency may contribute to higher respiratory complications in this population. The significant difference in respiratory distress severity underscores the importance of monitoring and managing Vitamin A levels in preterms.

SURFACTANT

In this study, 11.11% of preterm infants received surfactant therapy, while 88.89% did not. Surfactant therapy is used to treat or prevent RDS in preterm neonates by reducing the surface tension in the lungs and helping to keep the airways open. The relatively low percentage of infants receiving surfactant suggests that while RDS is a significant concern, it affects a smaller portion of the preterm infant population in this study. The majority of preterm infants (88.89%) not requiring surfactant therapy indicates that many infants either have sufficient natural surfactant production or do not develop severe RDS requiring this intervention. This is a positive indicator of most infants in the study.

In this study, none of the infants with normal Vitamin A levels required surfactant therapy, while 14.29% of those with Vitamin A deficiency and 15.69% of those with severe deficiency required surfactant therapy. No statistically significant association between the need for surfactant therapy and deficient and severe deficiency groups.

In this study, none (0%) of the infants with normal Vitamin A levels required surfactant therapy, while 15.38% of those with low Vitamin A levels required it. 100% of the infants with normal Vitamin A levels did not need surfactant therapy, compared to 84.62% of those with low Vitamin A levels. P-value of 0.038, indicates a statistically significant association between low cord blood Vitamin A levels and the requirement of surfactant therapy.

XRAY

In this study, majority (77.78%) of preterm infants had normal chest X-ray findings, while a smaller proportion had varying degrees of Hyaline Membrane Disease (HMD): HMD 1 (5.56%), HMD 2 (5.56%), HMD 3 (11.11%). 77.78% of the infants had normal X-ray findings is encouraging, suggesting that the majority of the preterm infants did not develop significant respiratory complications that would be visible on an X-ray. However, the presence of HMD in 22.22% of the infants (grades 1, 2, and 3 combined) highlights the need for continued vigilance and appropriate respiratory support.

In this study, for infants with normal Vitamin A levels, all (100%) had normal X-ray findings. Among those with Vitamin A deficiency, 78.57% had normal X-ray findings, 7.14% had HMD (Hyaline Membrane Disease) grade 2, and 14.29% had HMD grade 3. For infants with severe Vitamin A deficiency, 66.67% had normal X-ray findings, 9.8% had HMD grade 1, 7.84% had HMD grade 2, and 15.69% had HMD grade 3. Results from this study indicates a non significant trend towards higher HMD scores in severe deficiencies(p-value=0.06), whereas various degrees of HMD were present in 30.76% of those with low Vitamin A levels. This difference reached statistical significance(p-value= 0.02)

RDS

In this study, 22.22% of preterm infants were diagnosed with RDS, while 77.78% did not develop RDS. The relatively high percentage of infants not developing RDS (77.78%) is a positive outcome, suggesting that many preterm infants did not experience severe respiratory complications. However, the 22.22% of infants who did develop RDS highlights the ongoing risk and need for effective respiratory support and monitoring in this population. These infants required interventions such as CPAP, ventilator support, or surfactant therapy to manage their condition.

In this study, none (0%) of the infants with normal Vitamin A levels developed RDS, whereas 21.43% of those with Vitamin A deficiency and 33.33% of those with sevcre Vitamin A deficiency developed RDS. Among the infants with normal Vitamin A levels, 100% did not develop RDS. 78.57% of those with Vitamin A deficiency and 66.67% of those with severe deficiency did not develop RDS. Statistically significant association between the occurrence of RDS and cord blood Vitamin A levels was seen. This finding suggests that lower Vitamin A levels in preterms are significantly associated with a higher incidence of RDS. Infants with Vitamin A deficiency or severe deficiency are more likely to develop RDS compared to those with normal Vitamin A levels. This underscores the importance of monitoring Vitamin A levels and addressing deficiencies to potentially reduce the risk of RDS in preterm infants.

According to Chen HJ et al., Retinol deficiency within 48 hours of birth associated with an increased risk of severe RDS (estimated OR, 2.949; 95% CI, 1.285-6.767; p=0.011).[5]

HYPERBILIRUBINEMIA

In this study, 42.22% of the preterm infants were diagnosed with hyperbilirubinemia, while 57.78% did not develop this condition. The relatively high percentage of infants diagnosed with hyperbilirubinemia (42.22%) suggests that this is a significant concern among preterm infants in the study. Majority of babies (57.78%) not developing hyperbilirubinemia is a positive outcome, indicating that more than half of the preterm infants did not experience severe jaundice requiring medical intervention.

In this study, among infants with normal Vitamin A levels, 20% developed hyperbilirubinemia, while 80% did not. For those with Vitamin A deficiency, 42.86% developed hyperbilirubinemia, while 57.14% did not. Among infants with severe Vitamin A deficiency, 52.94% developed hyperbilirubinemia, while 47.06% did not. There is statistically significant association between the occurrence of hyperbilirubinemia and cord blood Vitamin A levels.

In Tao E et al., no significant association between low cord blood Vitamin A levels and hyperbilirubinemia. [4] In Chen HJ et al., no significant association between UCB Vitamin A levels and hyperbilirubinemia reported.[5]

SEPSIS

In this study, 14.44% of the preterm infants were diagnosed with sepsis, while 85.56% did not develop this condition. The relatively low percentage of infants diagnosed with sepsis (14.44%) is a positive finding, indicating that the majority of preterm infants (85.56%) did not experience sepsis. among infants with normal Vitamin A levels, 4% developed sepsis, while 96% did not. For those with Vitamin A

deficiency, 7.14% developed sepsis, while 92.86% did not. Among infants with severe Vitamin A deficiency, 21.57% developed sepsis, while 78.43% did not. There is no statistically significant association between the occurrence of sepsis and cord blood Vitamin A levels.

In Tao E et al., no significant association between low cord blood Vitamin A levels and the occurrence of sepsis. [4] In Chen HJ et al., no significant association between low retinol concentrations and risk for sepsis.[5]

LIMITATIONS

- The sample size of 90 preterm infants may be insufficient to detect smaller but clinically significant association between Vitamin A levels and various neonatal morbidities. Larger sample sizes can help in confirming the findings.
- As this study was conducted at a single center, this might limit generalizability of the results in other populations or settings. Multicenter studies would provide a broader perspective.

CONCLUSION

- Majority of preterm infants have low Vitamin A levels, with 72.22% in low category compared to 27.78% with normal levels.
- No significant correlation between gender with cord Vitamin A levels (p=0.517).
- No significant difference in birth weight(p=0.668) or gestational age among groups (p=0.539).
- Significant association with cord blood Vitamin A levels ($p < 0.001$); higher deficiencies in LSCS deliveries.
- No significant differences in APGAR scores at l and 5 minutes across Vitamin A levels (p=0.423 and p=0.390, respectively).
- Significant association of respiratory distress with Vitamin A levels ($p<0.001$); higher Modified Downe scores associated with lower levels of Vitamin A.
- Significant association with cord blood Vitamin A levels ($p < 0.001$); higher deficiencies required more oxygen support, more CPAP and ventilator support for longer duration(p=0.048).
- None of the infants with normal Vitamin A levels required surfactant while 14.29% with deficiency and 15.69% with severe deficiency required surfactant therapy.
- Significant association with cord blood Vitamin A levels ($p = 0.005$); higher deficiencies had more RDS cases; surfactant need and X ray changes found more in low Vitamin A group.

- Sepsis did not show significant difference (p=0.086) although it was more prevalent in low Vitamin A group (18.5%) compared to the normal group (4%)
- Significant correlation with cord blood Vitamin A levels (p = 0.024); higher deficiencies had more hyperbilirubinemia cases.

SUMMARY

The study reveals a significant prevalence of Vitamin A deficiency among preterm neonates, showing more than half of the infants with severe deficiency. Key findings indicate that lower umbilical cord blood Vitamin A levels are significantly associated with increased risk of RDS, hyperbilirubinemia, and the need of extended oxygen therapy, CPAP support and longer duration of ventilator support.

Additionally, there is a notable association between the mode of delivery and Vitamin A levels, with cesarean sections linked to higher rates of Vitamin A deficiency. Although there was no significant association with ventilator requirement, sepsis, the borderline p-values suggest that further research with larger sample sizes may be warranted.

RECOMMENDATIONS

Overall, these findings underscore the importance of monitoring and addressing Vitamin A deficiency among premature neonates to potentially decrease incidence of related morbidities and improve neonatal outcomes. Vitamin A supplementation at birth might be beneficial in infants at risk to have Vitamin A deficiency especially neonates delivered via cesarean section, preterms who are at risk to develop respiratory distress syndrome, hyperbilirubinemia, sepsis. According to WHO's guidelines on newborn care, it is suggested that infants should receive single oral dose 50,000 international units of Vitamin A in first 48 hours of delivery. This recommendation aims at preventing Vitamin A deficiency, which might be crucial for reducing the risk of morbidities. Our study supports the fact that this recommendation might be beneficial in practice.

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ANNEXURE I:

INFORMED CONSENT FORM

"CORD BLOOD VITAMIN A LEVELS IN PRETERMS AND IT'S ASSOCIATION WITH EARLY NEONATAL PERIOD MORBIDITIES- A PROSPECTIVE COHORT STUDY"

Name of Student/Principal Investigator: _____

Name of Guide/Co Investigators: _____

OBJECTIVES:

PRIMARY OBJECTIVE: To explore the association between vitamins A levels in preterms and early neonatal period morbidities.

SECONDARY OBJECTIVES:

1. To determine the prevalence of low vitamin A levels in preterms.
2. To analyze the potential factors that may affect umbilical cord vitamin A levels.

Introduction: as per the recent research, vitamin A levels in cord blood in preterms might have an association with the early neonatal period morbidities for which WHO is suggesting a birth dose of Vitamin A supplementation. Hence this study will be carried out to check this association as well as the prevalence of low vitamin A levels in preterms.

Explanation of procedure: After selecting the study participants who fulfil the inclusion criteria,

3ml umbilical cord blood specimens to be collected after cord has been cut and clamped, preserved in anticoagulant tubes , centrifugated at 2000-3000 RPM.

Vitamin A levels to be measured with enzyme linked immunosorbent assay(ELISA) vitamin A kits.

Follow up study will be done for the preterm neonates for first 7 days of life(Early neonatal period).

During follow up relationship between UCB vitamin A levels and morbidities such as1 min APGAR<7, hospitalization, oxygen supplementation, hyperbilirubinemia, RDS and sepsis will be observed as per the proforma.

Withdrawal from participation in the study: Participation in this study is voluntary. You will be free to decide whether to participate in this study or continue participation once enrolled. In case you decide to withdraw your participation, you are free to do so. However, please convey the decision to the principal investigator.

Possible benefits from participating in the study: You will/will not have nor get any benefits by participating in this study. The data gathered will help the population at large.

Possible risks from participating in the study: There are no risks involved in participating in this study.

Privacy and confidentiality: The information collected from you will be coded, to prevent any person from identifying you. Your identity will never be revealed. The data collected from you will be kept confidential and only processed or aggregated data will be used for publication.

Financial incentives: You will not receive any payment for participating in this study.

Authorization for publication of aggregated data: Results obtained after processing of the aggregated data will be published for scientific purposes and or presented to scientific groups. However, your identity will never be revealed.

Questions: In case of any questions with regard to this study, you are free to contact: **REG NO BM0121019** Department of Paediatrics, KLE Academy Of Higher Education And ResearchJawaharlal Nehru Medical College, Belagavi-590010, Karnataka

If you have any question or complaints with regard to your right as study participantyou may contact Dr Harsha Hegde, Chairperson, Ethical committee of JNMC, 0831-2473777 Extension 4052.

Legal rights: By signing this consent form, we are not waving any of your legal rights.

ANNEXURE II : PROFORMA

Name:

1. Age of mother:

2. Mode of delivery: NVD/LSCS/Assisted

3. Infant details:

Ip number: DOB:

Sex: Male/Female

Gestational age:

Birth weight :

4. Resuscitation Details:

Cried at birth : Yes/No

Any intervention :

APGAR : /10 (1min) /10 (5min) /10 (10min)

5.Early neonatal outcome: Modified Downe's scoring system (On admission)

Score	0	1	2
Respiratory rate (rate/min)	<60	60-80	>80
Cyanosis	None in room air	No cyanosis onoxygen support	Cyanosis inspite of oxygen support
Retractions	None	Mild	Moderate to severe
Grunting	None	Audible with stethoscope	Audible without stethoscope
Air entry	Good	Decreased	Barely audible

Score:

O2/CPAP/ Ventilator requirement:

Duration:

Surfactant:

RDS: Yes/ No

6.Umbilical cord blood vitamin A level:

7.NICU admission: YES/NO

Reason for NICU shift:

8.Hyperbilirubinemia: Yes/No

9.Sepsis: Yes/no

ANNEXURE III: MASTERCHART

Sl No	Name	Gender	Birth weight	Gestational age	Mode of delivery	Apgar at 1 min	Apgar at 5 mins	Oxygen need for >24hrs	CPAP requirement	CPAP(No of days)	Ventilator requirement	Ventilator(No of days)	Modified downe scoring	Surfactant	X ray	RDS	Hyperbilirubinemia	Sepsis	UCB Vitamin A level
1	B/O Rajshree twin 1	Male	2.46	34 weeks 3 days	LSCS	7	8	Yes	Yes	1	No	0	2				Yes	No	0.221
2	B/O Rajshree twin 2	Male	2.12	34 weeks 3 days	LSCS	6	9	No	No	0	NO	0	0				Yes	No	0.342
3	B/O Laxmi Anil twin1	Female	1.7	34 weeks 1 day	LSCS	7	9	No	No	0	No	0	0				No	No	0.229
4	B/O Laxmi Anil twin 2	Male	1.6	34 weeks 1 day	LSCS	7	9	No	No	0	No	0	0				Yes	No	0.589
5	B/O Mohini	Male	2.5	35 weeks	NVD	7	10	No	No	0	No	0	0				No	No	1.871
6	B/O Varsha triplet 1	Female	1.1	31 weeks 5 days	LSCS	8	9	Yes	Yes	2	No	0	3				No	No	0.523
7	B/O Varsha triplet 2	Female	1.25	31 weeks 5 days	LSCS	7	8	Yes	Yes	1	No	0	3				Yes	Yes	0.469
8	B/O Varsha triplet 3	Female	1.3	31 weeks 5 days	LSCS	8	9	No	No	0	No	0	0				Yes	No	0.32
9	B/O Afreen	Female	1.6	34 weeks 1 day	LSCS	6	9	No	No	0	No	0	0				No	No	0.371
10	B/O Pradnya twin 1	Male	1.6	33 weeks 4 days	NVD	6	8	Yes	Yes	1	No	0	4				No	Yes	0.2
11	B/O Pradnya twin2	Female	1.56	33 weeks 4 days	NVD	7	9	No	No	0	No	0	0				Yes	No	0.288
12	B/O Shridevi twin 1	Male	1.05	29 weeks 1 day	LSCS	6	8	Yes	Yes	3	Yes	1	7	1 dose on day 1 of life	HMD 3	Yes	Yes	Yes	0.279
13	B/O Shridevi twin 2	Male	1	29 weeks 1 day	LSCS	6	8	Yes	Yes	3	Yes	1	6	1 dose on day 1 of life	HMD3	Yes	No	No	0.34
14	B/O Sushma twin1	Male	1.45	30 weeks 3 days	NVD	7	8	Yes	No	0	No	0	2				No	No	0.796
15	B/O Sushma twin 2	Female	1.52	30 weeks 3 days	NVD	8	9	No	No	0	No	0	0				Yes	No	0.22
16	B/O Ashwini twin1	Female	1.75	34 weeks 1 day	LSCS	6	9	Yes	Yes	1	No	0	3				Yes	Yes	0.306
17	B/O Ashwini twin2	Male	1.8	34 weeks 1 day	LSCS	7	9	No	No	0	No	0	0				Yes	No	0.359
18	B/O Shilpa twin 1	Male	1.68	34 weeks 3 days	LSCS	6	8	Yes	No	0	No	0	2				No	No	0.236
19	B/O Shilpa twin 2	Female	1.72	34 weeks 3 days	LSCS	8	9	No	No	0	No	0	0				No	No	0.287
20	B/O Sonali	Male	2.5	35 weeks 1 day	NVD	8	9	No	No	0	No	0	0				No	No	0.73
21	B/O Akshatha Gaudar	Male	2.45	34 weeks 5 days	NVD	8	10	No	No	0	No	0	0				Yes	No	0.33
22	B/O Kasturi	Female	1.36	30 weeks	NVD	6	8	Yes	No	0	No	0	2				No	No	1.043
23	B/O Yogita	Male	2.9	35 weeks	NVD	7	9	No	No	0	No	0	0				No	No	0.24
24	B/O Veena Patil	Male	2	33 weeks 5 days	NVD	7	8	No	No	0	No	0	0				No	No	0.767
25	B/O Vaijanta	Female	2.72	35 weeks 2 days	NVD	7	9	No	No	0	No	0	0				Yes	Yes	0.22

26	B/O Karemma	Male	1.45	33 weeks 6 days	LSCS	8	9	Yes	Yes	2	Yes	3	5	1 dose on day 1 of life	HMD 3	Yes	Yes	Yes	0.25
27	B/O Sukanya	Female	1.18	29 weeks 1 day	LSCS	7	9	No	No	0	No	0	0				No	No	0.23
28	B/O Sevanti	Male	1.15	31 weeks	LSCS	4	8	Yes	Yes	1	Yes	3	6	1 dose on day 1 of life	HMD 3	Yes	No	No	0.352
29	B/O Rohini triplet 2	Male	1.3	31 weeks	LSCS	7	9	Yes	Yes	1	No	0	2				Yes	No	0.209
30	B/O Ambika twin 1	Male	1.51	30 weeks 5 days	LSCS	8	9	Yes	Yes	2	No	0	2				Yes	No	0.178
31	B/O Shahnaz	Male	1.01	29 weeks 5 days	LSCS	8	9	Yes	Yes	2	No	0	2		HMD 2	Yes	No	No	0.14
32	B/O Yashoda	Female	2.7	34 weeks 1 day	NVD	7	9	No	No	0	No	0	0				No	No	0.703
33	B/O Laxmi Prasad	Male	2.4	35 weeks	NVD	7	9	No	No	0	No	0	0				Yes	No	0.71
34	B/O Ashwini Sawanth	Male	2.64	34 weeks 3 days	NVD	8	9	No	No	0	No	0	0				Yes	No	0.518
35	B/O Pooja Gadiger	Female	2.34	35 weeks	LSCS	6	8	Yes	No	0	No	0	2				No	Yes	0.225
36	B/O Sheethal	Female	2.1	33 weeks 5 days	LSCS	7	9	No	No	0	No	0	0				Yes	No	0.339
37	B/O jyoti gopal	Male	2.4	33 weeks 6 days	LSCS	6	8	Yes	Yes	2	No	0	6		HMD1	Yes	Yes	No	0.21
38	B/O Parimala	Male	1.4	32 weeks 2 days	LSCS	6	7	Yes	Yes	2	No	0	3		HMD 3	Yes	Yes	No	0.217
39	B/O Akshatha Pare	Female	2.6	35 weeks 2 days	LSCS	7	9	No	No	0	No	0	0				No	No	0.482
40	B/O Poonam	Female	1.3	31 weeks 1 day	LSCS	7	9	Yes	Yes	4	No	0	5		HMD2	Yes	No	No	0.2
41	B/O Nakusha twin 1	Female	1.7	36 weeks	LSCS	6	8	Yes	Yes	2	No	0	3				Yes	No	0.175
42	B/O Akshatha Gaudar	Male	1.7	33 weeks 2 days	NVD	7	9	No	No	0	No	0	0				No	No	0.97
43	B/O Sangeetha	Male	2	33 weeks	LSCS	7	9	No	No	0	No	0	0				No	No	0.337
44	B/O Neeta	Female	2.35	34 weeks 4 days	NVD	8	9	No	No	0	No	0	0				No	No	1.064
45	B/O Anha	Male	2.2	34 weeks 2 days	NVD	7	8	No	No	0	No	0	0				No	Yes	1.778
46	B/O Tanzeela	Female	1.85	33 weeks 4 days	NVD	6	8	Yes	Yes	1	No	0	2				No	No	0.459
47	B/O Nakusha twin 2	Female	1.6	36 weeks	LSCS	7	9	No	No	0	No	0	0				Yes	No	0.282
48	B/O Ambika twin 2	Female	1.15	30 weeks 5 days	LSCS	7	9	No	No	0	No	0	0				No	No	1.64
49	B/O Afifa	Male	1.8	32 weeks 5 days	LSCS	6	9	Yes	Yes	1	No	0	2				Yes	No	0.34
50	B/O Jayashri	Male	1.9	34 weeks	LSCS	6	8	Yes	Yes	2	No	0	2				No	No	0.28
51	B/O Sumayya	Male	2	33weeks 2 days	LSCS	6	8	Yes	Yes	2	No	0	5		HMD1	Yes	No	Yes	0.13
52	B/O Shagufta	Female	2.1	35 weeks 6 days	LSCS	8	9	Yes	Yes	1	No	0	2				Yes	No	0.345
53	B/O Padma Teli	Male	3.4	34weeks	LSCS	7	8	Yes	Yes	2	No	0	2				No	No	0.285
54	B/O Rajlalakshmi	Female	1.26	30 weeks 3 days	LSCS	2	6	Yes	Yes	3	Yes	1	6	1 dose on day 1 of life	HMD3	Yes	No	Yes	0.14
55	B/O Sangamma	Female	1.6	32 weeks 5 days	NVD	6	8	No	No	0	No	0	0				No	No	0.892
56	B/O Priyanka Desai	Male	2.1	33 weeks 6 days	LSCS	7	9	No	No	0	No	0	0				No	No	0.24
57	B/O Kaveri	Female	1.8	34 weeks 1 day	LSCS	7	9	Yes	Yes	2	No	0	0		HMD 2	Yes	Yes	No	0.18
58	B/O Indumathi twin 2	Female	1.4	33 weeks 3 days	NVD	6	8	No	No	0	No	0	0				Yes	No	0.71
59	B/O trupthi	Female	2	34 weeks	NVD	6	8	No	No	0	No	0	0				No	No	0.72
60	B/O Suneeta Koth	Male	2.1	35 weeks 1 day	LSCS	5	8	Yes	No	0	No	0	2				No	No	0.4
61	B/O Vijaylaxmi	Female	1.4	32 weeks 2 days	LSCS	7	8	Yes	No	0	No	0	2				Yes	No	1.29
62	B/O Roopa Patil	Male	2.9	34 weeks 2 days	LSCS	8	9	Yes	Yes	2	Yes	5	5				Yes	No	0.21
63	B/O Tahseen	Female	1.7	33 weeks 5 days	NVD	7	8	Yes	No	0	No	0	2				No	Yes	0.25
64	B/O Nikhat	Female	0.8	28 weeks 1 day	NVD	7	9	No	No	0	No	0	0				No	No	0.78

65	B/O Deepa Dyamangouda	Female	1.69	31 weeks	LSCS	6	7	Yes	Yes	3	Yes	4	6	1 dose on day 1 of life	HMD3	Yes	Yes	No	0.55
66	B/O Nameetha	Male	2.7	34 weeks 5 days	LSCS	7	9	No	No	0	No	0	0				No	No	0.298
67	B/O Shantatai	Male	1.13	29 weeks 2 days	LSCS	2	6	Yes	Yes	1	Yes	2	6	1 dose on day 1 of life	HMD3	Yes	Yes	No	0.32
68	B/O Sangeeta	Female	1.8	31 weeks 5 days	NVD	7	8	Yes	Yes	1	No	0	2				Yes	Yes	0.16
69	B/O Ujjwala	Male	1.59	32 weeks 5 days	NVD	6	8	Yes	No	0	No	0	2				No	No	0.74
70	B/O Safeena	Female	1.34	35 weeks 4 days	LSCS	7	9	Yes	Yes	2	No	0	2				No	No	0.16
71	B/Surekha	Male	1.4	33 weeks 3 days	LSCS	6	8	Yes	Yes	2	No	0	5		HMD1	Yes	Yes	No	0.26
72	B/O Supriya	Male	1.8	33 weeks	LSCS	6	8	Yes	Yes	2	No	0	6		HMD1	Yes	No	No	0.22
73	B/O Indumathi twin 1	Male	1.48	33 weeks 3 days	NVD	7	8	No	No	0	No	0	0				Yes	No	0.23
74	B/O Shivaleela	Male	1.9	34 weeks 2 days	LSCS	6	8	Yes	Yes	1	No	0	2				No	No	0.32
75	B/O Rohini triplet 3	Female	1.2	31 weeks	LSCS	7	9	Yes	Yes	2	No	0	3				Yes	No	0.31
76	B/O Asima	Male	2.2	34 weeks 2 days	LSCS	6	8	Yes	Yes	1	Yes	2	6	1 dose on day 2 of life	HMD2	Yes	No	No	0.25
77	B/O Pradnya	Male	1	29 weeks 6 days	LSCS	6	7	Yes	Yes	2	Yes	5	6	2 doses on D1 and D2 of life	HMD 3	Yes	Yes	No	0.14
78	B/O Nameeta	Female	1.5	32 weeks 4 days	NVD	7	9	No	No	0	No	0	0				Yes	No	0.97
79	B/O Shama	Female	2.2	35 weeks 1 day	LSCS	6	9	No	No	0	No	0	0				No	No	0.74
80	B/O Sameena	Male	1.8	34 weeks 2 days	NVD	6	9	No	No	0	No	0	0				No	No	0.703
81	B/O Akshata Patil twin 1	Male	1.6	35 weeks 2 days	LSCS	7	9	Yes	No	0	No	0	2				No	No	0.54
82	B/O Akshata Patil twin 2	Male	1.5	35 weeks 2 days	LSCS	6	9	No	No	0	No	0	0				Yes	No	0.71
83	B/O Sudha	Male	2.6	32 weeks 5 days	LSCS	2	7	Yes	Yes	1	Yes	3	7		HMD2	Yes	No	No	0.398
84	B/O Suvarna	Male	2.6	36 weeks	NVD	7	9	No	No	0	No	0	0				No	No	1.15
85	B/O akshata	Male	1.32	28 weeks 6 days	LSCS	6	8	Yes	Yes	2	Yes	2	6	1 dose on day 1 of life	HMD3	Yes	No	No	0.325
86	B/O Priyanka	Female	2.54	36 weeks 1 day	NVD	7	9	No	No	0	No	0	0				No	No	0.89
87	B/O Heena	Female	1.6	34 weeks 2 days	NVD	7	10	No	No	0	No	0	0				Yes	No	0.52
88	B/O Rukkaiya	Male	2.1	33 weeks 4 days	NVD	6	9	No	No	0	No	0	0				No	No	0.72
89	B/O Nikita	Male	1.25	29 weeks 5 days	NVD	5	8	Yes	Yes	2	No	0	6		HMD1	Yes	No	Yes	0.22
90	B/O Neeta	Female	1.85	31 weeks 2 days	NVD	7	9	No	No	0	No	0	0				No	No	1.04