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NUTRITION IN LOW BIRTH WEIGHT INFANTS

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NUTRITION IN LOW BIRTH WEIGHT INFANTS

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CHANGING TRENDS IN THE MANAGEMENT OF LOW BIRTH WEIGHT INFANTS

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Infants born at less than 2500 g are usually termed as Low Birth Weight (LBW) infants. Traditionally this group of infants were termed as high risk group infants in terms of neonatal mortality and morbidity. However in the current day scenario of modern neonatology, the at risk group of babies are actually the Very Low Birth weight (VLBW) and Extremely Low Birth Weight (ELBW) infants who are less than 1500g and less than 1000g respectively. This article mainly addresses problems related to the VLBW and ELBW infants who constitute a special group of babies with increased risk of mortality and morbidity in the Neonatal Intensive Care Unit.

VLBW survival has improved with the widespread use of surfactant agents, maternal steroids, and advancements in neonatal technologies. The minimum age of viability is now as young as 24 weeks, with scattered reports of survivors born at 22-23 weeks' estimated gestational age.

Although survival rates have better correlation with gestational age, if one compares survival based on birth weight there has been a substantial improvement in survival figures over the last decade which has been reported in developed countries. Survival figures from the National institute of child health and human development neonatal network was 34% at less than 751 g birth weight 66% at 751 through 1000 g, 87% at 1001 through 1250 g, and 93% at 1251 through 1500 g (1). There was a marked improvement in the survival figures in the lower gestational age, with survival of almost 23% at 23 weeks, 34% at 24 weeks, and 54% at 25 weeks (1).

Survivability correlates with gestational age for infants who are appropriately grown (AGA). ELBW infants are more susceptible to all of the possible complications of premature birth, both in the immediate neonatal period and after discharge from the nursery.

Although the mortality rate has diminished, the proportion of surviving infants with severe sequelae, such as chronic lung disease, cognitive delays, cerebral palsy, and neurosensory deficits (i.e., deafness and blindness), has not.

Aetiology

The primary causes of VLBW are premature birth (born <37 weeks gestation, and often <30 weeks) and intrauterine growth restriction (IUGR), usually due to problems with placenta, maternal health, or to birth defects. Many VLBW babies with IUGR are preterm and thus are both physically small and physiologically immature.

Any baby born prematurely is more likely to be very small. However, other factors that can contribute to the risk of VLBW include:

- Age: Teen mothers (especially if <15 years old) have a much higher risk of having VLBW infant.
- Multiple birth babies are at increased risk of being VLBW because they often are premature. More than 50% of twins and other multiple gestations are VLBW.
- Maternal health: Women exposed to drugs, alcohol, and cigarettes during pregnancy are more likely to have LBW or VLBW babies. Mothers of lower socioeconomic status are also more likely to have poorer pregnancy nutrition, inadequate prenatal care, and complications of pregnancy. All are factors that can contribute to VLBW.

Neonatal problems and management

Neonatal complications are markedly increased in VLBW, and especially in ELBW infants. Because most VLBW infants are also premature, it may be difficult to differentiate problems due to prematurity from those due to very small size. In general, the lower a baby's birth weight, the greater are the risks for complications. However, some complications of prematurity (*e.g.*, risk of RDS) are lessened by the stress of mild to moderate intrauterine growth restriction. Clinical problems associated with VLBW and ELBW include:

1. Hypothermia

LBW infants have higher body surface area:body weight ratios, decreased stores of brown fat and glycogen, and may not be able to conserve or generate body heat. Clinical problems associated with hypothermia include hypoglycaemia, apnoea, increased oxygen consumption and metabolic acidosis.

Prevention of hypothermia increases survival of the infants. Methods of preventing heat loss include:

- a. Drying the infant at birth to prevent evaporative heat loss
- b. Warmed blankets or plastic wraps to prevent convective and radiant heat loss during transport
- c. Swaddling to preserve body heat in the more mature infants, and radiant heater or incubator to maintain a neutral thermal environment for smaller infants

2. Hypoglycaemia

Hypoglycaemia results due to decreased stores of glycogen and fat. Hypothermia and hypoxia aggravate this due to increased metabolic demands and anaerobic glycolysis. Methods of preventing hypoglycaemia are:

- a. Prevent hypothermia which can exacerbate hypoglycaemia
- b. Early enteral feeding where indicated
- c. Recognising the need to start dextrose infusion in those babies where early enteral feeding is not possible

3. Fluid and electrolyte imbalances

Compared with full-term newborns, VLBW infants have proportionally more fluid in the extracellular fluid compartment than the intracellular compartment and a larger proportion of their body weight is attributable to water (2). During the early days after birth, diuresis may result in a 10-20% weight loss, which can be exacerbated by iatrogenic causes, such as radiant warmers and phototherapy. Fluid status is commonly monitored with daily (or sometimes twice daily) body weights, strict recording of fluid intake and output and frequent monitoring of electrolytes.

ELBW infants also have compromised renal function stemming from a decreased glomerular filtration rate and a decreased ability to reabsorb bicarbonate which may result in metabolic acidosis. Hypernatremia and hyponatremia are common in VLBW infants, reflecting disturbances of free water relative to total body sodium. Hypo and hypernatraemia often result due to a disorder of water rather

than sodium. As these infants are exposed to radiant heat, phototherapy, and the relatively dry environment, substantial amounts of free water may be lost, causing a relative increase in sodium concentrations. Management of hypernatremia in ELBW infants consists of administration of hypotonic fluid (plain dextrose solutions without any additives) to replace the free water loss, perhaps requiring as much as 150 - 200 ml/kg/day to maintain adequate hydration. On the other hand, hyponatremia in the first few days of life may be the result of excess free water resulting in a dilutional hyponatremia and restriction of fluid and sodium supplementation may be the appropriate treatment (2).

4. Nutrition

In the current day scenario of modern neonatology the two most serious problems encountered by the VLBW and ELBW infants are sepsis and nutrition. There has been a lot of interest and development in the feeding and nutrition of the VLBW and hence has been addressed in detail as a separate article (Feeding Low Birth weight Infants – Current challenges and trends) in this issue about low birth weight infants.

Initiating and maintaining growth of VLBW infants is a continuing challenge. The growth rate often lags because of complications such as respiratory distress, feed intolerance and sepsis. Concern that early feeding may be a risk factor for necrotizing enterocolitis (NEC) often defers initiation of enteral feeding, although nutritional management of such infants is marked by a lack of uniformity of practice.

Parenteral nutrition which is commonly referred to as TPN (Total Parenteral Nutrition) may provide the greater source of energy in ELBW infants in the first few weeks after birth. Although referred to as TPN, in practice it is most likely to be partial parenteral nutrition since most of these infants will be on variable amount of enteral feeds at any given time and hence will be addressed as just Parenteral Nutrition (PN) in this article. Optimal PN in India is usually obtained by using separate infusions of amino acids, dextrose with or without electrolytes and lipids. In developed countries PN may be obtained as a combined infusion of amino acids, dextrose, minerals, electrolytes and trace elements with the lipids available as a separate infusion.

Enteral feeding can begin as early as day 1 (provided infant is medically stable), using small-volume

trophic feeding (approximately 10 ml/kg/d) to stimulate the gastrointestinal tract and prevent mucosal atrophy (3). If tolerated, as evidenced by minimal gastric residuals and clinical stability, feeding may increase by as much as 10-20 ml/kg/d. Although feeding practices vary widely, not only from region to region but also in the same unit from one clinician to the other.

Clinical studies across the world have consistently demonstrated that infants who are fed earlier and are advanced according to a feeding plan achieve full enteral feeds sooner than their counterparts, who are treated less systematically with a conservative approach. Although the fear of precipitating NEC remains widespread, randomized controlled trials have repeatedly failed to show any relationship between feeding practices (i.e., age at initiation, rapidity of advancement, caloric density) and the occurrence of NEC. The only feeding practice that has consistently shown to have a protective effect against NEC is the use of breast milk instead of formula feeds (4). However despite its many nutritional and immunological advantages, sometimes in the ELBW group of infants it may not provide sufficient quantity of energy, proteins, calcium and phosphorus to maintain adequate growth rate and bone mineralization. To facilitate this more often than not breast milk may have to be fortified using Human Milk Fortifiers (HMF), which can be added to breast milk to make it nutritionally adequate for the ELBW infant. Potential complications of human milk fortifiers include increased osmolarity and bacterial contamination. Evidence shows that although there may be some benefit using HMF in the short term, like improved weight gain, head circumference and linear weight gain, in the long term there was no difference in neurodevelopmental outcome and there is no evidence to suggest there are no deleterious effects with HMF (5). In those instances when mother's milk is unavailable, banked breast milk or specially formulated preterm formulas may have to be used. The whole aim of nutritional management is to mimic in utero growth of the VLBW infants which in practise is easier said than done.

5. Sepsis

Due to a number of advancements in the respiratory management (antenatal steroids, surfactant, high frequency ventilation and nasal CPAP), sepsis has now become the single most important cause of neonatal mortality and morbidity in the VLBW and ELBW group of infants. Sepsis may either be early-onset or late-onset depending upon the timing of the onset of sepsis, following birth. Early-onset

sepsis usually occurs within the first 48-72 hr after birth and is almost always related to maternal genital tract colonization. The commonly implicated organisms are Escherichia coli, Klebsiella and Group B streptococcus.

Late-onset infections typically occur after the first week of life and result from endogenous hospital flora (nosocomial). Organisms responsible for late-onset infections are Coagulase Negative Staphylococcus (CONS), Klebsiella, Pseudomonas and E. Coli. Majority of these infections are catheter related infections usually secondary to placement of endotracheal tubes, umbilical lines and central lines. These infections to a great extent can be prevented by adopting a non invasive approach of managing babies such as using nasal CPAP, avoiding placement of umbilical and central lines and adopting a policy of minimal handling and strict hand washing.

Clinical signs of infection in this group of babies are extremely non specific, and include temperature instability (hypothermia or hyperthermia), tachycardia, decreased activity, poor perfusion, apnoea, bradycardia, feeding intolerance, increased need for oxygen or higher ventilatory settings, and metabolic acidosis. Laboratory studies that may help in the diagnosis of infection would include Complete Blood Count (CBC), C reactive protein (CRP), low platelet count, procalcitonin, neutrophil banding, blood culture, urine culture and cerebrospinal fluid culture. One should have a low threshold for starting antibiotics (blood cultures should always be taken before starting antibiotics or before changing antibiotics), but an even lower threshold to stop the antibiotics once the blood cultures are negative after 48 hr.

Since infections are extremely common in the NICU, there is a low threshold for using antibiotics which has resulted in an evolving trend of multidrug resistant organisms. In order to prevent this problem all institutions should have a strict antibiotic policy based on the local microbiological surveillance of the unit. It is imperative to have first line antibiotics for infections occurring in the first 72 hr of life and second line antibiotics for infections occurring after the first 72 hr, since the causative organisms are quite different (as mentioned above). First line antibiotic combinations commonly used are a penicillin with an aminoglycoside and second line antibiotic combinations would include cloxacillin with aminoglycoside or tazobactam/piperacillin combinations. One would consider using Vancomycin if there is a central line in situ. Antibiotics should be used sensibly in conjunction with blood culture and sensitivity results. Third generation Cephalosporins as routine antibiotics should be

used with extreme caution due to the emergence of Extended Spectrum Beta Lactamases (ESBL), resulting in multidrug resistance. Oral antibiotics have no role in the prevention or treatment of sepsis in the neonatal period.

6. Necrotising enterocolitis

Necrotising enterocolitis (NEC) is a condition especially seen in the VLBW and ELBW infants. Incidence of NEC is directly correlated with decreasing gestational age and low birth weight. It is much more common in Intra uterine growth retarded (IUGR) babies especially those who have altered Doppler flows, such as absent or reversal of flow (indicating chronic hypoxia/compromise). NEC is said to be multifactorial in origin and its exact aetiology is poorly described, with hypoxia, rapid increase in feeds, type of feeds and sepsis all being implicated as causative factors. The role of enteral feeding in NEC remains extremely controversial, however there is some evidence that breast milk is protective but does not prevent NEC.

Presenting signs and symptoms of NEC are non specific, and in clinical practice often difficult to differentiate from sepsis. They include apnea, bradycardia, large gastric residuals, metabolic acidosis, lethargy, abdominal distention and sometimes passage of blood in the stools. Radiographic findings may help in confirming the diagnosis, and this may include thickened loops of bowel, pneumatosis intestinalis (presence of gas in the bowel wall), portal venous gas, and free air indicating perforation of the bowel - an ominous sign of impending deterioration.

Management of NEC without perforation is usually non surgical – which includes keeping the infant nil by mouth, periodic gastric decompression by nasogastric tube and broad spectrum antibiotics. In practice most VLBW infants who develop NEC are extremely unwell and may require ventilatory support, fluid resuscitation and circulatory support in the form of inotropes. They may also require supportive measures to correct complications such as metabolic acidosis and thrombocytopenia. Since most babies with NEC will be nil by mouth for prolonged periods (two – three weeks) it is absolutely essential to support their nutritional needs with Total Parenteral Nutrition (TPN), so that they do not slide into a catabolic state. Surgical intervention may become necessary if evidence of perforation exists (presence of free air on radiographs) or medical treatment fails or if there is severe abdominal distension that is affecting mechanical ventilation (abdominal drain insertion). NEC requiring surgery

is associated with high mortality and morbidity. Long term problems include malabsorption syndromes – short gut syndrome, strictures and abdominal adhesions.

7. Hyperbilirubinemia

Most ELBW infants develop clinically significant hyperbilirubinemia (jaundice) requiring treatment. Hyperbilirubinemia develops as a result of increased red blood cell turnover and destruction in the context of an immature liver that has physiologically impaired conjugation and elimination of bilirubin. In addition, most preterm infants have reduced bowel motility due to inadequate oral intake, which delays elimination of bilirubin-containing meconium, coupled with increased enterohepatic circulation of conjugated bilirubin that enters the intestinal tract. All the above reasons, coupled with the fact that VLBW infants have an immature blood-brain barrier (BBB), puts these infants at a greater risk of developing kernicterus when compared to term infants. Kernicterus occurs when free, unconjugated bilirubin crosses the BBB and stains the basal ganglia, pons, and cerebellum; diminished protein status and the occurrence of acidosis in ELBW infants may potentiate the proportion of unbound bilirubin available to cross the BBB. Although death is a rare consequence of kernicterus in the present day scenario, babies who do survive, do so with dire sequelae such as mental retardation and cerebral palsy. Phototherapy is used to decrease bilirubin levels to prevent the elevation of unconjugated bilirubin to levels that cause kernicterus. Special blue lamps with wavelengths of 420-475 nm are used to break down unconjugated bilirubin to the more water-soluble product lumirubin via photoisomerization and photooxidation through the skin. This product can then be eliminated in bile (stools) and urine, thereby decreasing the serum levels of unconjugated bilirubin and preventing the occurrence of kernicterus.

Newer phototherapy lights such as CFL and biliblanket have been developed which have decreased the insensible losses in babies requiring phototherapy, however it is important to closely monitor the fluid and electrolyte balance in the VLBW and ELBW group of babies. Another important precaution that should be taken is to shield the baby's eyes so as to prevent overexposure to light. The exact level at which phototherapy should be initiated depends on the gestational age and the postnatal age of the infant. Specific age related charts have been published by the American Academy of Pediatrics which can be used as a guide to start and stop phototherapy. A more simple method that can be used when

bilirubin is measured as $\mu\text{mol/l}$ (conversion to mg/dl is to divide by 17) is – gestational age $\times 10 =$ level for exchange transfusion and subtract 100 = level to commence phototherapy. For example for a 28 week gestation baby the exchange transfusion level would be $28 \times 10 = 280 \mu\text{mol/l}$ or 16 mg/dl ($280/17$) and the level to commence phototherapy would be $280 - 100 = 180 \mu\text{mol/l}$ or 10.5 mg/dl . Use of prophylactic phototherapy has not been shown to decrease the peak level of total serum bilirubin (TSB) or the duration of phototherapy.

Exchange transfusion is an invasive procedure and is associated with complications such as electrolyte imbalances (hypocalcaemia, hyperkalaemia), acidosis, thrombosis, sepsis and bleeding and hence needs to be carefully deliberated before embarking on.

8. Respiratory Distress Syndrome

An early complication of VLBW and ELBW infants is surfactant deficiency Respiratory Distress Syndrome (RDS). The correlation of RDS is stronger with gestational age rather than the birth weight of the infant per se. The incidence of RDS is inversely related to the gestational age, i.e. the lesser the gestational age higher the incidence of RDS. In babies who are born small for gestational age there is a decrease in the incidence of RDS. Following is a chart of the incidence of RDS as per the gestational age in infants born to mothers who have not received antenatal steroids.

Clinical signs of RDS include tachypnea (>60 breaths/min), cyanosis, chest retractions, nasal flaring, and grunting. Untreated RDS results in increasing difficulty in breathing and increasing oxygen requirement over the first 24-72 hours of life. Chest radiographs reveal a uniform reticulogranular pattern with air bronchograms. As a result of surfactant deficiency, the alveoli collapse, causing a worsening of atelectasis, edema, and decreased total lung capacity. There has been a significant decrease in the incidence and complications associated with RDS, due to a number of advancements in the respiratory management of these infants.

Some of the significant advances in the last one to two decades have been;

- a.** Introduction of antenatal steroids
- b.** Surfactant replacement therapy

- c. High Frequency Oscillatory Ventilation (HFOV)
- d. Non invasive nasal Continuous Positive Pressure (CPAP)

The incidence of RDS in preterm infants has been significantly reduced with the use of antenatal steroids to promote lung maturity—an additive effect was seen with the use of both antenatal steroids and early surfactant treatment. There has been a lot of debate regarding the use of surfactant therapy – synthetic surfactant Vs natural surfactant and prophylactic surfactant Vs rescue surfactant. There is now enough evidence to suggest that natural surfactants are much more superior to synthetic surfactants and are associated with lesser mortality and fewer complications such as pneumothorax (6). The evidence is so very compelling that synthetic surfactants are hardly ever used in modern day neonatology. There has been considerable amount of debate regarding the use of prophylactic surfactant as opposed to rescue therapy. Meta analysis in the Cochrane review has shown a decrease in mortality and some complications when prophylactic surfactant has been used in infants born at less than 28 weeks gestation, however they did not show a significant decrease in the rate of Chronic lung disease (7). Till more evidence is available it may be wise to use prophylactic surfactant in infants less than 28 weeks gestation, however if used as prophylactic treatment, surfactant should be administered as soon after birth as possible to get the maximum benefit. In infants greater than 28 week gestation surfactant can be used as rescue treatment - a reasonable approach is to treat most infants as soon as clinical signs of RDS appear, or if the respiratory picture does not improve after the initial ventilatory management.

Another important strategy in the management of RDS, that has evolved over the last few years has been early use of nasal CPAP which has decreased the need for ventilation in the VLBW and ELBW infants (8).

9. Intraventricular haemorrhage

The incidence and severity of intraventricular haemorrhage (IVH) is inversely related to the gestational age, i.e. lower the gestation higher the occurrence of IVH. IVH is rarely seen in babies above 32 weeks gestation since the germinal matrix is better developed and less likely to result in a bleed and hence is a condition mainly seen in the ELBW infants.

The pathophysiology of IVH is quite complicated, but the haemorrhage usually begins in the periventricular subependymal germinal matrix and then progresses into the ventricular system. IVH is more likely to occur in extremely preterm babies because development of the germinal matrix

typically is incomplete and the protective cerebral autoregulation present in older babies has not yet developed. Any perinatal event such as hypoxia, ischemia, rapid fluid changes, rapid changes in blood pressure (hypo/hypertension), sepsis and pneumothorax that results in disruption of vascular autoregulation can result in IVH. In most cases IVH is asymptomatic, however occasionally it may present with apnoea, blood pressure instability, acidosis and sudden drop in haemoglobin. Seizures are an extremely rare presentation of IVH in a preterm infant.

All preterm infants born at less than 32 weeks gestation should be screened for IVH, which can be done as a bedside cranial ultrasound scan. The cranial ultrasound scan should be done by an experienced doctor, which may be a neonatologist or a radiologist. Ideally these babies should have at least two cranial ultrasound scans, the first done as soon after birth as possible and the second at 6 weeks postnatal age. Although it is most practical to describe the IVH as seen on the ultrasound scan the most preferred system is to classify them into grades, as follows

- a. Grade I - Germinal matrix haemorrhage
- b. Grade II - IVH without ventricular dilatation
- c. Grade III - IVH with ventricular dilatation
- d. Grade IV - IVH with extension into the parenchyma

Babies with grade III IVH and above, will need close monitoring with weekly or fortnightly cranial ultrasound scans and weekly head circumference measurements to monitor the development of hydrocephalus. In most cases of grade I and II there is spontaneous resolution of IVH without any neurological sequelae, nevertheless any baby with IVH should have an MRI scan at follow up to look for resolution of IVH, myelination of the internal capsule and the periventricular white matter.

Improving the quality of neonatal care is the only method in preventing or decreasing the incidence of IVH. The risk of IVH is higher in infants who are transported after birth, underlining the need for preterm births to occur at centers specializing in high-risk deliveries. To decrease the incidence of IVH personnel trained in neonatal resuscitation should attend preterm deliveries, and one should also avoid hypocarbia, hypoxia and rapid alterations in the mean arterial blood pressures. Some trials have shown a decrease in IVH when antenatal steroids have been used.

10. Anaemia of prematurity

The physiologic anaemia seen in term infants occurs earlier and is more profound in preterm infants. Anaemia of prematurity is extremely common in VLBW and ELBW babies and may result because of

- blood loss secondary to multiple blood draws in the first few weeks of life, a developmentally immature erythropoietic response to anaemia, decreased survival of red blood cells in preterm infants. Treatment of anaemia in preterm infants includes transfusion of packed cells (RBC), the usual volume of transfusion being 20ml/kg over a period of 4-6 hr, which usually raises the haemoglobin by approximately 4gm/dl. Administration of iron or recombinant erythropoietin has not shown to prevent anaemia or the requirement of blood transfusion in the first few weeks of life in the ELBW infants. It is extremely rare for an ELBW infant not to receive a blood transfusion during their stay in the NICU. One should however minimise the number of blood transfusions to avoid the risk of transfusion borne infections. This can be achieved only if the neonatal units adopt a policy of minimal blood draws and strict transfusion policy i.e. delay transfusions until infant develops symptoms rather than based on threshold haematocrit values.

11. Retinopathy of prematurity

Retinopathy of prematurity (ROP) is a disease of the premature retina which has not yet been fully vascularised. Exposure of the premature retina to various stimuli such as supplemental oxygen and light have been postulated to cause a disruption in the natural course of vascularisation which may lead to abnormal proliferation of blood vessels resulting in retinopathy. If premature babies are not screened for ROP and treated appropriately it may result in retinal detachment and blindness. All premature babies \leq 31 weeks gestation or birth weight less than 1500g should be screened for ROP. Screening should commence at 6 weeks postnatal age or 36 weeks postmenstrual age whichever occurs first. Screening is a continuous process and should be done at intervals of every 10 – 14 days, till the baby has reached 42 weeks postmenstrual age (Term + 2 weeks – corrected age) (9).

If ROP is present, its stage and location will dictate management, which usually entails laser therapy to the affected retina. Infants with ROP are also at greater risk for sequelae, such as myopia, strabismus, and amblyopia and should have ophthalmology follow up till 1 -2 years of age. ELBW infants without ROP should also have a follow-up eye examination at age 6 months because of the risk of myopia.

Follow up care of VLBW and ELBW infants

Nearly all VLBW and all ELBW babies will need close neonatal follow up following discharge from hospital. Most of these infants typically have complicated medical courses and often go home with multiple treatments and medications, hence it is extremely important to not only have good paediatric

follow up but a well organised neurodevelopmental follow up. The goals of the neonatal follow-up clinic are early identification of developmental disability; parental counselling; identification and treatment of medical complications. The neonatal follow up clinic should ideally be supported by a multidisciplinary team consisting of physiotherapist, speech therapist and an occupational therapist in addition to a developmental paediatrician. The multidisciplinary approach should be provided under one roof with good co-ordination between the teams so as to decrease the number of visits by the patient. There should be a provision for feedback to the neonatologist and obstetrician, from the follow up team so that these healthcare providers are aware of their outcomes and can make necessary changes to practice when indicated.

As part of neurodevelopmental follow up it is necessary to evaluate cognitive development, vision, hearing and milestones. With ever improving neonatal care and non invasive approach most of these infants do not develop severe handicaps but are prone to have minor problems such as behavioural and cognitive problems and most of them reach their milestones at least by their corrected age. Nevertheless these infants have a higher incidence of cerebral palsy and mental retardation when compared to the general population. Infants at the greatest risk of having these problems are the ones who have had abnormal cranial findings such as grade III or IV IVH, periventricular leukomalacia, abnormal myelination of the internal capsule and thalamic/basal ganglia changes (10).

The long term follow up study of the EPICure study found that infants born before 26 weeks gestation had significant cognitive and neurologic impairment at school age. The study was conducted in the United Kingdom and had 241 patients, which were compared with 160 classmates born at full term. Interestingly they found that 38% of the preterm infants who did not manifest any disability at 30 months progressed to moderate to severe disability by the time they reached school age (11). Keeping this in mind it is extremely important to continue neurodevelopmental follow up till late into childhood, as opposed to the current practice of following these children till 2 -3 years of age.

Immunisation

Preterm infants are at increased risk of experiencing complications of vaccine-preventable diseases but are less likely to receive immunizations on time. There has been considerable debate and confusion regarding the timing of vaccinations in the VLBW and ELBW infants. The American Academy of Pediatrics (AAP) policy of immunisation of the preterm and low birth weight infants, goes a long way in terms of addressing this issue (12). The policy clearly states that all preterm infants who are medically stable should receive vaccines at the appropriate chronological age as per the schedule that is recommended for full term babies. There should be no delay in administering the

routine vaccines and the full dose of the vaccine should be administered to the preterm infant. The only exceptions being the BCG vaccine and Oral polio vaccine, both of which being live vaccines are better administered at the time of discharge from the unit. There is also some evidence to administer the Hepatitis B vaccine after 30 days of life in preterm infants weighing less than 2000 g , since it is believed to have a less than satisfactory immunogenic response when administered before this. Apart from these exceptions all vaccines routinely recommended during infancy are safe for use in preterm and LBW infants. The occurrence of mild vaccine-attributable adverse events are similar in both full-term and preterm vaccine recipients.

These babies in addition to the usual immunisations may also be offered optional vaccines such as conjugated pneumococcal vaccine and influenza vaccine (babies with chronic lung disease/ prolonged ventilation), based on individual unit policies.

Parent counselling

This is a very important but often ignored aspect of care of the VLBW and ELBW infants. The birth of an extremely premature infant brings a unique kind of stress to a family dynamics. These infants go through a lot of ups and downs during their stay in the NICU and the parents often experience wide swings of emotion during this period. They go through different stages of grief, from denial to acceptance and as care giver one should be sensitive to their needs. Counselling should ideally start (whenever possible) even before the delivery of the child so that the neonatologist can prepare them for their infants long and arduous journey in the NICU. Care givers must be frank and take time to explain to parents the various different stages the infant may pass during their stay. The whole neonatal team (doctors and nurses) should be considerate to the emotions experienced by the parents and should be prepared to provide additional support to the family.

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Feeding the Low Birth Weight infant – Current challenges and trends!

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Feeding the preterm or low birth weight (LBW) infant is an ever challenging prospect in the neonatal intensive care unit. With better understanding of the needs and requirements of these infants, feeding practices have evolved and changed on a constant basis so as to simulate growth patterns in utero. Although there has been considerable amount of data published regarding the short term effects of feeding the LBW infant, only recently has there been any data published regarding the long term effects of early nutrition, which may affect the health and development of the LBW infant.

Human breast milk, as the sole enteral feed for preterm or low birth weight infants, has a number of advantages with regard to delivering immuno-protective factors such as secretory immunoglobulin-A, lysozyme and lactoferrin and in improving the mother-infant interaction (American Academy of Pediatrics and Workgroup on Breastfeeding 1997). Case-control data suggest a decreased incidence of adverse outcomes such as feed intolerance or significant gastrointestinal disease in infants nourished with human breast milk compared with formula milk (1). However, the nutritional requirements - calories, protein and minerals - of these infants, who are born with relatively impoverished nutrient reserves and are subject to additional metabolic stresses compared with term infants, may not be fully met by enteral feeding with human milk (2). These deficiencies may have adverse consequences with regards to the growth and bone mineralization. Early postnatal nutrition during a very vulnerable period of brain growth may also affect later neurodevelopment (3). All these factors puts it into perspective, the important role nutrition plays not only in the short term but also in the long term growth and developmental outcome in the preterm or LBW infant. This article tries to address certain basic principles of feeding the LBW infant such as the caloric need, type of feed, route of feed administration and the feeding schedule of these infants.

Nutritional need of the LBW infant

An international consensus statement, based on data from growth and nutrient balance studies, has recommended energy, protein and mineral intakes to support intra-uterine growth rates for stable/growing preterm and LBW infants (4). Energy requirements are approximately 120 kcal/kg/day with a corresponding protein input of 3 gm/kg/day to provide the optimal protein:energy ratio. If feeding at 180 ml/kg/day, the milk will

require an energy content of at least 68 kcal/100ml and a corresponding protein concentration of 1.7- 2.1 gm/100ml. The recommended intakes of calcium (80- 120 mg/kg/d) and phosphorus (60- 140 mg/kg/day) are required to support intra-uterine accretion rates and to avoid metabolic bone disease due to mineral deficiency.

The milk feed of the LBW infant will also need to have 6 – 7 g (per 100ml of milk) of carbohydrate which should ideally be in the form of lactose and should have at least 4.2 to 4.6 g of lipids some of which should be in the form of medium chain triglycerides (MCT).

In addition to these major components of milk, the LBW infants also have a higher requirement of vitamins, minerals and trace elements, than their full term counterparts. Deficiency of these micronutrients may lead to improper myelination, slow brain growth and inadequate mineralization of the bones in the LBW infant, all of which may affect the long term growth and development of these infants.

Choice of milk

A wide range of diets (milk) have been used to feed the preterm or LBW infant. Some of the commonly used milk are:

- Human breast milk
 - Mothers own preterm milk
 - Banked donor milk
- Fortified human milk (banked/mothers breast milk)
- Term infant formulas
- Special preterm infant formulas

Human breast milk

The use of human breast milk in the feeding of the preterm/LBW infant is invaluable. The practice of encouraging mothers to provide breast milk for their own preterm/LBW infant has become widespread. One cannot stress the importance of providing breast milk as the main source of early feeding for the LBW infant. Human milk has a number of protective advantages over formula feed, especially so in the LBW infants.

In a developing country like ours, where infection rates are very high, the anti infective property of breast milk plays a very important role and in addition to this it is extremely

economical when compared to using term/preterm formulas. Some studies have shown that preterm babies fed exclusively on formula feeds had six times more incidence of confirmed Necrotising enterocolitis (NEC) when compared to preterm infants fed exclusively on breast milk (5). Although larger randomised studies are required to confirm this finding, it is widely suggested that using human breast milk (mother's own/banked milk) may decrease the incidence of NEC. It has also been suggested that the incidence of feed intolerance is much lower in breast fed infants than formula fed infants. It is a known fact that breast milk has lower intragastric transit time compared to formula feed and this may be responsible for better feed tolerance and vomiting in this group of infants. Feed tolerance is extremely important in the pathway towards establishment of full enteral feeds, so as to provide the LBW infant adequate nutrition for proper growth and development. Some studies have shown that formula fed babies take substantially longer to establish full enteral feeds when compared to exclusively breast milk fed babies (6). Further, studies have shown that preterm babies fed their own mothers milk had higher developmental scores at 18 months and also better Intelligence quotient at 7-8 years when compared to formula fed preterm infants (7).

One can safely predict that human breast milk is far superior in all aspects than any other form of feeds for the preterm/LBW infant apart from the fact that it may not always meet the theoretical requirements of the LBW infant in providing adequate Nutrients such as proteins, calories, sodium, calcium and phosphate, trace elements and vitamins. However human milk has the added nutritional advantage about the type and composition of fat (DHA and omega fatty acids) and better bioavailability and absorption of these compared to formula feed. There is also some evidence to suggest that although the constitution of trace elements and vitamins is less in breast milk, the bioavailability of these is far superior to formula feed. If one is overtly concerned about the nutrition of an individual LBW infant one can always add HMF to breast milk so as to increase the nutritional value.

Human breast milk may be in the form of the mothers own breast milk or banked donor milk (BDM). The milk of mothers who have delivered preterm has a different composition from that of mothers delivered at term. Preterm milk (PTM) has higher concentration of protein nitrogen, sodium and trace elements when compared to term breast milk. In view of all these reasons, PTM is more suitable for feeding preterm babies and is even better than feeding with donor banked milk. Whenever possible it is always recommended to first feed the baby with mothers own PTM and the balance milk should then be provided with BDM (whenever this is available) or with a preterm formula feed. Mothers should always be encouraged to express their own milk (PTM) and nurseries should provide provision for expressing milk such as breast pump and adequate storage

facilities to store the expressed milk.

There is now considerable amount of evidence to state that banked donor milk (BDM) is the next best method of feeding the preterm/LBW infant, after mothers own breast milk. Although human milk banking is extremely common in developed countries it is still in its very primitive form in India, with very few banks available providing a comprehensive service. Ideally milk banks should have a good collecting system where donor milk is collected from mothers who have been tested for transmittable diseases (HIV, hepatitis B and C, CMV etc), then bacterially decontaminated (pasteurised), microbiologically tested, stored safely (frozen) and then thawed adequately before using it for the preterm infant. Because of this processing BDM may lose some of the nutrient value, especially so in terms of calories, vitamins and trace elements when compared to preterm milk, however it is still considered to be far superior, than preterm formula milk because of better feed tolerance and decreased incidence of NEC.

Fortified human milk

A novel method to overcome some of the nutrient deficits in human breast milk (either PTM or BHM) is to add human milk fortifier (HMF). HMF is currently available in the powdered form and this can be added to a specified amount of human milk, so as to improve the nutritional content. It usually provides extra amount of calories, proteins, calcium and phosphate, trace elements and huge range of vitamins that are necessary for the preterm/LBW infant. The only theoretical problem with HMF is that the composition of breast milk is extremely variable and the addition of HMF may sometimes result in a disproportionate increase in the nutritional value of the breast milk (especially in terms of osmolality and solute load) which may be detrimental to the LBW infant. It is hence advisable not to use HMF in the early stages of feeding but can be used once full enteral feed (120 – 150 ml/kg/day) has been established. Again HMF should be used with discretion, by the attending physician based on the weight gain, calcium and phosphate values and nitrogen balance of each individual LBW infant.

A meta analysis for the Cochrane collaboration concluded that use of HMF was associated with short term improvements in weight gain, linear growth and head circumference but there was no evidence of long term benefit in growth and insufficient evidence to state that there were no deleterious effects (8). Although further large studies are required, the concept of human milk fortification, both mothers as well as banked milk is promising and offers the potential benefit of feeding the LBW infant with human milk while avoiding the possible nutrient deficiencies of breast milk on its own. Since one of the primary goals of nutrition in the LBW infant is to try and achieve in utero

growth rates, we in our unit use HMF along with human milk if the infant's weight gain is unsatisfactory, once full enteral feed has been established.

Term infant formula

For a number of years and even today in some places people are using term formulas to feed preterm/LBW infants. Such formulas have been designed for term babies whose nutritional requirements, are quite different to that of the LBW infant and is hence best avoided. They contain a lot less protein, energy, calcium and phosphate, sodium, trace elements and vitamins when compared to preterm formulas and, to meet the energy requirement of the LBW infant, they will need to be fed in excess of 200 ml/kg /day which most infants may struggle to tolerate. Data from large trials have shown that LBW infants fed with term formula grow a lot more slower than their counterparts fed with preterm formula and also have substantially lower mental and developmental scores at 18 months (9). In view of all this evidence, in the current day scenario there is no role for term formula in the feeding of the LBW infant, and one should use a preterm formula to feed these infants when breast milk is not available.

Preterm infant formula

A number of specialised preterm/LBW infant formulas have been introduced into clinical practice in the last few years. There may be quite marked variations among the various preterm formulas in their composition, in terms of energy/calories provided, protein, lipids and trace elements. However most of these preterm formulas should theoretically meet the nutritional requirements of the LBW infant and are more appropriate than the term formula feeds for this special group of infants. Moreover the preterm formula feeds are constantly evolving (based on information from clinical trails), so as to suit the needs of the LBW infants.

Some clinical trials have shown that preterm formulas may have number of short term advantages over unfortified human milk, in that they promote growth i.e. faster weight gain, linear growth and head circumference (10). They have also shown to reduce hospital stay, bone disease of prematurity, hypophosphataemia and some vitamin deficiencies (11). One of the potential problems of using preterm formula compared to human milk is the problem of inducing a metabolic strain i.e. it increases the renal solute load and protein overload, especially so in the very low birth infant and the sick preterm infant. Although it may be nutritionally superior in terms of calories and proteins it is still advisable to start enteral feeds in the LBW infants with either mother's own breast milk or human banked milk. Preterm formulas may be used later as a supplement to aid growth in those infants who fail to do so on fortified or unfortified human milk, or on those rare

occasions when no human milk is available.

Continuous Vs intermittent bolus feeding

Most preterm/LBW infants born before 32 – 34 weeks gestation, in the early stages are usually fed using a nasogastric or orogastric tube. There has been considerable amount of debate whether babies receiving tube feeds (TF) should have continuous TF or intermittent bolus TF. Each of these methods have their advantages and disadvantages and have been subjected to a number of meta analysis, the most comprehensive being the review by the Cochrane collaboration in 2004. Continuous TF have the advantage of being more energy efficient by increasing energy absorbed and decreasing energy expenditure (12), reduce feeding intolerance, improve nutrient absorption, and improve growth and there are some theories to suggest that it may reduce feed related apnoea and bradycardia. However, continuous infusion of milk into the gut could alter the cyclical pattern of release of gut hormones which might affect metabolic homeostasis, and growth and also may exacerbate reflux in these infants.

Milk feedings given by the intermittent bolus TF are thought to be more physiologic because they promote the cyclical surges of gut hormones normally seen in healthy term infants (13). Surges in plasma concentrations of these gut hormones postnatally may be important for gut development. However due to the functional limitations of the premature infant's gut such as delayed gastric emptying or intestinal transit could hinder the premature infant's ability to handle bolus milk feeds, resulting in feed intolerance. Additionally, this feeding regimen alternates between periods of feeding and fasting which may not simulate in utero conditions (gut is receiving nutrition on a continuous basis through the placental circulation) and may hence result in decreased growth.

The Cochrane review did not show any difference in either continuous or intermittent bolus feeds with regards to important nutrition related parameters such as growth, necrotising enterocolitis, time to reach full enteral feeds and feed intolerance (14). As of now there is little evidence to recommend one over the other, and we ourselves recommend intermittent bolus feeds (2 – 3 hourly) simply because it is technically easier and cost effective when compared to continuous feeds which requires paraphernalia like the infusion pump.

Early Vs late feeds

The best time to begin feeding milk to premature or low birth weight babies is not known. Necrotizing enterocolitis (NEC) is a life-threatening bowel illness in newborn babies born prematurely. As there is concern that feedings in the gastrointestinal tract may increase the risk of NEC, some babies receive only intravenous nutrition for prolonged periods. However, there is also a concern that delaying feedings could lead to growth and feeding problems. Enteral feedings in very low birth weight or sick preterm infants are often delayed for several days or weeks after birth even though delayed enteral feeding could diminish the functional adaptation of the gastrointestinal tract and result in feeding intolerance later. Early initiation of feedings could promote growth and shorten the duration of parenteral nutrition and hospital stay, provided it did not increase the risk for NEC. The Cochrane review does not currently support one method of feeding over the other since there are no large randomized studies to evaluate early vs. late feeding. Some benefits of early feedings were noted in one study -- fewer days on parenteral nutrition, fewer infants who were treated with gastric suction and interruption of feedings, fewer infants with sepsis evaluations, and fewer infants with percutaneous central venous catheters (15).

We as a policy in our unit believe in early enteral feeds and usually start feeds at the rate of 10ml/kg/day, on day 1 of life and thereon tend to increase feeds at the rate of 10ml/kg twice a day. We usually aim to reach full enteral feeds by the end of the first week to 10 days of postnatal life. The only exception to this rule of early enteral feeds is if the baby is at increased risk of NEC such as abnormal maternal Doppler's (absent /reversed end diastolic flow in the umbilical artery), severe IUGR or sepsis. Our experience, by adopting the above policy with early enteral feeds is decreased need for parenteral nutrition, decreased need for invasive lines, decreased incidence of sepsis/suspected sepsis, lesser feed intolerance, lesser cost and more importantly better growth.

Summary

Evidence suggests that human breast milk has an important role to play in the management of the LBW/preterm infant. There is now increasing evidence to suggest that using human milk results in earlier and faster establishment of full enteral feeds, thereby decreasing the use of parenteral nutrition, decreased incidence of sepsis and decreased length of hospital stay and decreased cost of neonatal care. The use of breast milk is most likely associated with a reduction in the incidence of NEC and systemic infection. LBW infants only on breast milk may show poor growth initially and in these

group of infants it is extremely important to promote growth and this can be achieved by fortifying milk using HMF. Poor early growth may have adverse consequences for short term survival, cognitive development and bone health. When mother's breast milk is not available one should try and use banked breast milk whenever available. If no breast milk (mothers or banked) is available then one should use specially formulated preterm formula as opposed to term formula feeds.

The primary aim of infant feeding in this group of babies is to start enteral feeds at the earliest and increase feeds consistently so that the baby is on full enteral feeds at the earliest possible time (usually 7 – 10 days postnatal age). Whether one uses continuous tube feeds or bolus tube feeds is immaterial as there is no evidence to suggest one is superior over the other.

However preterm infants are not a homogenous population and with increasing survival of the ELBW infants, nutrition plays an important role not only in terms of short term growth and survival but also in the long term development and quality of life in this group of babies. It is imperative that neonatal units formulate feeding policies and follow them consistently so as to objectively evaluate outcomes. Further work is required to explore different diets and how they can be tailored to individual babies needs.

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