ACHIEVING OPTIMAL FEEDS FOR PRETERM BABIES, RECOMMENDATIONS AND REALITIES IN PRACTICE: NIGERIAN PERSPECTIVE

A.I. Ayede

Department of Paediatrics, University College Hospital, Ibadan

Corresponding:
Dr. A.I. Ayede
Department of Paediatrics
University College Hospital
Ibadan

ABSTRACT

Preterm deaths are responsible for the highest number of neonatal mortality in Nigeria. Preterm nutrition contributes significantly to overall outcome particularly as it relates to neurodevelopment. Recently, new guidelines for enteral feedings in premature infants were issued by the American Academy of Paediatrics and European Society of Pediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. Nevertheless, in clinical practice it is often difficult to attain suggested intakes at all times. The situation is worse in Nigeria where there are no specific national guidelines and recommendations derived from local data targeting Preterms. There is a high possibility of significant potential cumulative nutritional deficits occurring in Nigerian preterms. The inevitable suboptimal intake contributes significantly to the incidence of neonatal diseases and outcome. This review describes practical ways of optimizing nutritional intake in these vulnerable neonates with reference to Nigerian situation. Understanding the preterm gut, initiation of parenteral nutrition, need for minimal enteral feeds, ensuring adequate macro and micronutrients intake and need for follow up are discussed. There are limitations to the practice of the recommended preterm nutrition in Nigerian settings, nevertheless the interventions like early commencement of minimal enteral feeds and preference for human breast milk should be practiced optimally. Hence, all health professionals should acknowledge that preterm nutrition may be an emergency and need to improve their knowledge on when and how to achieve optimal feeds in them. There is a dare need through both clinical practice as well as research, to reduce nutritional deficits in these vulnerable infants.

INTRODUCTION

Preterm deaths are responsible for the second highest number of neonatal mortality in Nigeria[1]. Preterm nutrition contributes significantly to their overall outcome particularly as it relates to neurodevelopment[2]. Feeding issues in preterm infants are a growing concern for neonatologists because of its contribution to outcome and the fact that attainment of independent oral feeding is one of the prerequisites for hospital discharge following their management. Weight gain, length and occipitofrontal circumference are routine parameters measured during the follow up management of preterm infants and their nutrition plays significant roles in these parameters. With the increase in survival of infants born preterm, understanding their nutritional needs have become paramount to newborn health care providers particularly neonatologists, paediatric gastro-enterologists and neurologists who follow up these babies on long term basis. Research over the last decade has begun to shed light on the development of oral feeding skills in these infants as they mature. This has increased understanding of their limited skills at varying postmenstrual ages. Such knowledge is crucial in clinical practice as expectations of these infants' oral feeding performance must take into account the ever-changing level of maturity of their skills. The role of gut immaturity in preterm infants is crucial and forms the basis for the mode of feeding, type of nutrient composition, combination and when to feed. The American Academy of Paediatrics and European Society for Paediatric Gastro- enterologist have given preterm recommendations based on in utero accretion growth rate and available data.

These recommendations however have their challenges even in developed countries and this is worse in developing countries like Nigeria[1]. This article reviews the practical aspect of these recommendations and discusses the challenges of implementing such in Nigeria.

The preterm gut peculiarities

The human fetus receives nutrients, growth factors and immunoglobulins via active or passive placental transport. The functional development of the gastro-intestinal tract begins in utero and continues into infancy while the fetal gut is anatomically complete by 20-22 weeks after conception. Nutrient transport systems are in place by 14 weeks for amino acids, 18 weeks for glucose and 24 weeks for fatty acids. Peristalsis begins at 28-30 weeks while coordination of suck, swallow and breathing is at 32-34 weeks. Colonization of the gut by bacteria and the introduction of nutrients into the gut affect postnatal gastrointestinal and immunological development. Swallowing of amniotic fluid nourishes the fetal intestine and prepares this organ for birth. Preterm delivery interrupts the transfer of these factors that are critical to prepare and protect the newborn infant from bacteria that will colonize the intestinal tract postnatally[3-5]. Preterm infants have anatomic and functional limits to the digestion and tolerance of enteral feeds. Oesophageal peristalsis is immature and bidirectional in preterms with forward movement of food to the stomach near term6. Intestinal motor activity is also immature and disorganized in preterm compare to term infants. Coordinated mature gastrointestinal motility and peristalsis with feeding develop in the preterm between 33 weeks to term. The more preterm a baby is, the greater the delay in passing the first stool. Enterokinase which is the rate limiting enzyme in the activation of pancreatic proteases has only 20% of term baby's activity in the preterm gut. Nevertheless, the preterm is able to digest and absorb protein efficiently because the protein digestion is aided by the activity of brush border and cytosolic peptidases. Carbohydrate absorption is on the other hand limited by the relative lack of lactase which is responsible for the breakdown of lactose into glucose and galactose. This lactase activity in preterm less than 34 weeks has about 30% of the activity seen in term babies. The relative lack of pancreatic lipase and a small bile acid pool size in preterm predispose them to malabsorb 10 – 30% of dietary fat[7].

Preterm nutritional recommendations

Breast milk is the preferred source of nutrients for newborn infants including the preterm, and the number of nutrients found in human milk is recommended as a guideline in establishing the minimum and maximum levels in infant formulas[8]. Sources of nutrient recommendations for preterm infants include the American Academy of Pediatrics Committee on Nutrition(AAP - CON), the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition (ESPGHAN - CON) and the Reasonable Ranges of Nutrient Intake published by Tsang and Colleagues. The overall goal is for the growth of the postnatal preterm infant, both their anthropometric indices and body composition to be the same as the normal fetus of the same gestational age growing in its mother's uterus[9]. These recommendations are based on the expected intrauterine growth rate, breast milk nutrient content, higher nutritional needs in preterm infants and data from normal biochemical parameters reflecting adequate intake.

Proteins and amino acids

Metabolic balance studies support a need for higher protein intakes in the growing preterm infant than in the term infant. The human milk is inadequate to meet the recommended 3.5 to 4g/kg/day for preterm babies[10]. Protein supplementation is beneficial for the growth of bone, brain and lean body mass unlike excess energy that leads to increased fat deposition[11]. Neurodevelopmental outcomes have been shown to be better in preterm infants fed with human milk fortified with protein and energy. These beneficial effects were even noted to have extended to adolescents whose brain size, caudate nucleus and intelligence quotient (IQ) were found to be directly proportional to their protein and energy intake during postnatal period[12-15]. Growth rate of the lean body mass is determined directly by the essential amino acids intake. Normal growth, energy metabolism and the immune function are known to depend on the availability of these essential amino acids.

Fat

Fetal fat deposition occurs in the last 12 – 14 weeks of gestation, thus the preterm infant are deficient in fat which is necessary for energy and thermogenesis. Dietary fats are important to sustain growth, provide essential fatty acids and promote the absorption of fat-soluble vitamins. Newborn infants absorb fat less efficiently than older children and fat digestion and metabolism is even less efficient in preterm infants. Lingual and gastric lipase as well as mammary gland lipase all compensate for the deficient pancreatic lipase. Current recommendations for dietary fat consist of 40% -52% of total calories which is equivalent to 4.4 – 5.7g/100kcal. Breast milk contains adequate arachidonic acid (AA) and docosahexaenoic acid (DHA) with the normal as 5 – 20mg/dL[16].

Carbohydrate

The predominant carbohydrate in human milk is lactose, a disaccharide composed of glucose and galactose. Glucose production rates among pre-term infants at about 28 weeks' gestation average about 6–8 mg/min/kg while among term infants average 3–5mg/min/kg[17,18]. Preterm infants in thermoneutral environment need 40 – 60kcal/kg/day to maintain body weight once adequate protein intake is achieved. These preterm infants need additional calories to maintain growth and the more preterm the infant is, the higher the calories required to achieve normal growth. Most preterm infants will attain adequate growth with calories of 130 – 150kcal/kg/day.

When to start feeding the preterm infant

Prior to the early 1960s, the usual practice was for preterm babies not to be fed in the first 24 hours as a result of the fear of aspiration from the feeble or absent sucking and swallowing[19]. A change in attitude was evident from the early 1960's when Victoria Smallpeice, the clinical director of the pediatric department at United Oxford Hospital, USA felt that it made no sense to stop supplying nourishment abruptly at birth when it was afforded continuously via the placenta as a fetus and began feeding undiluted human breast milk within the first 24 hours via an indwelling nasogastric tube[19]. Not providing enteral nutrition to very low birth weight infants (VLBWI) is nonphysiologic considering the fact that the fetus swallows about 150mL/kg/day of amniotic fluid during the last trimester of fetal development and this occurs without the occurrence of necrotizing enterocolitis (NEC) in utero[19]. The absence of food in the gastrointestinal tract is associated with mucosal and villous atrophy which leads to reduction of enzymes necessary for digestion and substrate absorption. The resulting decreased mucosal IgA from Peyer's patches and increased production of adhesion molecules and polymorphonuclear cell attraction have been shown to increase the incidence of systemic inflammatory response syndrome[20]. The anatomically and functionally immature intestine undergoes maturation fast if given the necessary stimulation in the form of feeding[21]. The current recommendation is to start minimal enteral feeds within the first 24 hours in preterm babies once they are stable. Prior to the stable period when full enteral feeds could be commenced, these infants should be preferably placed on parenteral nutrition[22].

Minimal enteral feeds

Minimal enteral nutrition is sub-nutritional quantities of milk feeds provided to prime the gut by stimulating many aspects of gut function. It is also known as trophic feeding or nutrition, gastrointestinal priming, gut priming and early hypocaloric feeding. It is a relatively recent concept that has been introduced into clinical practice in an attempt to counter the effects of enteral starvation[23, 24]. It may be defined as the practice of feeding nutritionally insignificant volumes of enteral substrate to neonates, to supply nutrients and directly stimulate developing gastrointestinal system without increasing disease severity. Typically, a milk volume of 10-20mL/kg per day is given at 2 hourly rates. Small amounts of feeds is given to supplement parenteral nutrition as early as the first day of life in infants <1,500 g at birth if the infant is stable. This has been found to provide a lot of benefits such as prevention of gastrointestinal atrophy, facilitation of gastrointestinal mucosal maturation, stimulation of the motor activity of the muscular layer of the gut, decreased cholestasis, and enhancement of the postprandial response. Other benefits include reduction of nosocomial infections and metabolic bone disease as well as decreased duration of hospital stay[25].

What to feed the preterm infant

Human milk is preferred for feeding term, preterm, and sick infants. In the absence of maternal breast milk, donor breast milk or preterm formula may be used in VLBWI after the initial few hours of intravenous fluid or parenteral nutrition. Extraordinary efforts should be made to use mother's own milk because the advantages of non-nutrient components in human milk are significantly diminished by storage and heat processing of the donor milk. Preterm maternal milk and banked milk provide insufficient amounts of energy, protein, sodium, calcium and phosphorus as well as other nutrients needed for rapid growth and normal development of the preterm infant. Human milk fortifier is indicated in preterm infants less than 31 gestational weeks and/or birth weight less than 1,500g. Fortification is commenced at volume of feeding at 100mL/kg/day[26].

The mother of the preterm infant should be encouraged to start expressing breast milk immediately after delivery. Maternal breast milk may lack some nutrients for the optimal growth of the VLBWI than preterm formula milk but confers important non-nutrient advantages for the preterm infant[26, 27]. Breast milk intake results in the release of endocrine and metabolic factors such as gastrin, entero-glucagon, motilin, neurotensin, gastroinhibiting peptide, and pancreatic polypeptide. Breast milk results in better absorption and motility along with stimulation of the growth of Bifidobacteriae and Lactobacillus strains. The predominance of whey protein and the mixture of amino acids in breast milk are compatible with the metabolic needs of the preterm infant. Digestion and absorption is improved compared to formula and breast milk also provides immunologic protection[27, 28]. The lower renal solute load facilitates better tolerance and a decreased risk of NEC and a significantly higher intelligence quotient at 8 years of age is another major advantage. Breast milk also contains omega 3 fatty acid that is alpha-linoleic acid from which other essential long chain polyunsaturated fatty acids (LCPUFAs), docosahexaenoic acids (DHAs) and arachidonic acid (AA) are produced. These play an important role in retinal and neurologic development[26,28].

Preterm formula is available to preterm infants whose mothers are unable to express sufficient breast milk. In general these formulas contain added whey protein, glucose polymers, and medium chain triglycerides, calcium, phosphorus, electrolytes, foliate, and fat soluble vitamins compared to term formula[26,29]. Preterm formulas may be used to supplement human milk feedings if the supply is inadequate. Formula derived from soy protein rather than animal casein and whey are unsuitable for premature infants[9]. Meta-analysis of eight clinical trials concluded that in preterm and low birth weight infants, feeding with formula milk resulted in a higher rate of short term growth but also a higher incidence of NEC. However, this was prior to the use of fortification of human milk and cannot be applied directly to current clinical practice but demonstrates the superiority and safety of breast milk for the preterm infants[26,30].

How to give enteral feeds in preterm

Premature infants are unable to coordinate sucking, swallowing, and breathing, hence orogastric tube-feeding is necessary. Orogastric route is better than nasogastric as the latter has been associated with an increase in airway resistance. The commonest methods used are continuous milk infusion and intermittent (bolus) milk delivery (usually every 2 hours for babies weighing less than 1.5kg and 3 hours for those weighing 1.5kg and above). Recent studies have suggested that bolus feeding promotes more "normal" feed-fasting hormonal concentrations that potentially benefit intestinal development and nutrient partitioning. Marked differences are also observed in feeding tolerance and growth between continuous versus bolus tube-feeding methods[26, 31-35].

Preterm nutritional supplements

Nutritional supplements are added to preterm feeds due to several reasons. These supplements include immunological substances such as nucleotides, prebiotics, probiotics and bifidobacteria. An additional energy supply with no concomitant increase in fluid volume is possible and supplementation results in an increase in short term weight gain, linear growth and head growth. Glucose polymers consist of polymers of glucose of various chain length and they have been used as nutritional supplements for infants because they have lower osmolarity per kilocalorie than glucose. In the newborn, the polymers are hydrolyzed by salivary, pancreatic, and intestinal amylases and maltases to free glucose[36]. Reduction or eliminations of lactose and replacement with the more readily digestible carbohydrate such as glucose polymers have been reported to improve feeding tolerance, weight gain, and calcium absorption. There are insufficient data to evaluate the effects of carbohydrate or fat supplementation on long term growth and development in preterm infants[37].

There is a high bioavailability of iron in breast milk but this is of limited value because of the low iron concentrations. Early postnatal anaemia is more pronounced in preterm than in term infants because erythropoiesis abruptly decreases after birth and the haemoglobin concentration declines rapidly at a rate of approximately 1g/dL/week. If adequate iron is not given postnatally, late anaemia of prematurity will begin to develop after 2 months of life[38]. The long term cognitive sequelae and shorter term motor sequelae of iron deficiency are notable. Iron is necessary for the normal development and functional integrity of the immune system. Insufficient amount of iron coupled with the high rate of postnatal growth calls for a higher iron requirement in LBWI. Premature infants weighing 1,000-2,000g require 2-3mg supplemental Fe/kg/day for 12-15 months. Recent recommendations for preterm infant formulas are a minimum of 1.7 to a maximum of 3.0Fe g/L. and the American Academy of Pediatrics recommends 2-4 mg/kg/day of enteral iron daily depending on the degree of prematurity between 2 weeks and 2 months[39]. Preterm infants show evidence of fat soluble vitamin deficiency from limited tissue storage at birth, intestinal malabsorption and rapid growth rates that increase requirements. Multivitamins should be started when full enteral feeding is established and continued until after discharge as needed[38].

Parenteral nutrition (PN)

In VLBW premature infants, enteral feeding cannot be fully established in the first few days due to immaturity of the gastrointestinal system. These infants will thus need PN particularly if they are critically ill, have undergone surgery or are having protracted diarrhoea. Fluid intake depends on environmental conditions and maturity of the infants. The average required energy for maintenance is about 50kcal/kg/day while about 70 kcal/kg/day is needed for optimal growth. This should be in form of 60% carbohydrate, 10-15% protein and 30% fat. The total kilocalories in 10% dextrose are 0.34 kcal/mL while 10% lipid solution contains 0.9% kilocalories/mL. Glucose is the most widely used intravenous carbohydrate for neonates because it is readily available to the brain. Glucose infusion should be at a rate of 4-6mg/kg per minute (6-8 g/kg per day) with progressive increase to 12-15 mg/kg per min (16-20g/kg per day)[40,41].

Protein requirements

The goal of giving proteins is to limit catabolism, maintain endogenous protein stores, and provide sufficient energy and protein to support growth. Parenteral nitrogen requirement is 30-35 mmol/kg per day, which is equivalent to 3.0-3.5mg/kg amino acids per day. These solutions contain nine essential amino acids and cysteine, tyrosine, taurine and arginine as the semi-essential amino acids. Many units will usually start amino acids at a rate of 1g/kg per day on the second day of life for extremely low birth weight (ELBW) infants and increase to 3g/kg per day with 1g/kg daily increments per day[40].

Lipid requirements

Parenteral fat is introduced at 1g/kg per day, and gradually increased to 3g/kg per day, given as a continuous infusion usually after the first three days. A 20% lipid emulsion is preferred over 10% emulsion, because the higher phospholipid content in 10% solution impedes plasma triglyceride clearance, resulting in higher concentrations of triglyceride and plasma cholesterol. Also, combined medium chain triglyceride (MCT)/long-chain triglyceride (LCT) and lipid emulsion is preferred over LCT emulsion in preterm and critical neonates, because MCT/LCT is more easily metabolized. Advantages of lipid emulsions over concentrated glucose solutions include their isotonicity and greater energy density, the latter means that a low volume is required per calorie.

Minerals, trace elements and vitamins

Minerals and trace elements delivered with PN are calculated to meet in-utero accretion rates. Sodium, potassium, chloride, calcium, magnesium and phosphorus levels need to be closely monitored and the infusion needs to be prescribed accordingly. Neonates on long-term total parenteral nutrition (TPN) may develop trace element deficiencies which should be checked regularly. The dose of water-soluble vitamins is 1mL/kg per day, which should be added to the dextrose-electrolyte solution. The dose of fat-soluble vitamins is 1mL/kg per day, which should be added to the lipid emulsions[40,41].

Preterm feeding practice in Nigerian settings and its implication

Little or no translational research has been done on preterm nutrition in Nigeria[1]. Despite the obvious roles of optimum nutrition in the growth, immunity and neurodevelopmental outcome of preterm infants, this aspect is greatly faced with many challenges when making attempt to practice optimal feeding in these infants. Late or no assessment by specialist may prevent early commencement of adequate parenteral nutrition. Even when such babies present in suitable centres with capable hands, the non-availability or non- affordability of suitable PN solutions will hamper the full implementation of such treatments. The resultant metabolic challenges will most of the time contribute significantly to poor preterm outcome particularly in terms of their neurodevelopment. The continuous scourge of human immune deficiency (HIV) virus infection and high cases of retroviral exposed babies many of whom are preterm has posed another significant challenge in preterm nutrition. Most mothers that opt for artificial feeds do so with the practice of mixed feeding, thus predisposing them to higher risk of infections, NEC, diarrhoea and HIV infection and all these tend to worsen the overall outcome (Ayede personal observation, unpublished data). The relatively high rate of HIV infection has also greatly limited the use of donor milk and pasteurization is not usually possible in most cases. The sole use of artificial milk is not culturally acceptable in most settings, thus facilitating mixed feeding which usually worsens the primary prognosis particularly in preterm infants. Breast milk fortification has been shown to be of tremendous benefit to preterm babies but this is hardly practiced in Nigeria as breast milk fortifiers are not usually available, are scarce or too expensive to bear by an average Nigerian. The poor socioeconomic status of most Nigerians and the fact that most Nigerians pay health bills out of pocket is a key fundamental problem[42]. All these no doubt are contributing to the high mortality and poor outcome of preterm birth in Nigeria.

CONCLUSIONS AND RECOMMENDATIONS

There are limitations to the practice of the recommended preterm nutrition in Nigerian settings, nevertheless the few proven interventions such as early commencement of minimal enteral feeds and preference for human breast milk should be practiced optimally. Therefore, it is crucial that all hospital staff acknowledge that preterm births' nutrition may be an emergency and need to improve their knowledge on when and how to achieve optimal feeds in them. There is a dare need through both clinical practice as well as in research to reduce nutritional deficits in these vulnerable infants. Continuous translational research in preterm nutrition and free health for pregnant mothers and children will play significant role in improving the impact of nutrition in preterm outcome.

REFERENCES

1. Saving newborn lives in Nigeria: Newborn health in the context of the integrated maternal, newborn and child health strategy, revised 2nd edition 2011, 1- 120.

2. **Smart JL.** Vulnerability of developing brain to under nutrition. Ups J Med Sci Suppl 1990;48:21–41.
3. **al Tawil Y,** Berseth CL. Gestational and postnatal maturation of duodenal motor responses to intragastric feeding. J Pediatr 1996; 129 (3): 374-379
4. **Caicedo RA,** Schanler RJ, Li N, *et al*. The developing ecosystem: implication to the neonate. Pediatr Res 2005;58 (4) : 625-629
5. **Mackie RI,** Sghir A, Gaskins HR. Developmental microbial ecology of the neonatal gastrointestinal tract. Am J Clin Nutr 1999; 69(Suppl): 1035-1040S,
6. **Jadcherla SR,** Duong HG, Hoffman RG *et al.* Esophageal body and upper esophageal sphincter responses to esophageal provocation during maturation in preterm newborn. J Pediatr 2003;143: 31- 35.
7. **Manson WG,** Weaver LT. Fat digestion in the neonate. Arch Dis Child Fetal Neonatal Ed 1997; 76: F206 -211.
8. **Mattar CN,** Chan YS, Chong YS. Breastfeeding: it's an important gift. Obstet Gynecol 2003;102: 1414-1418.
9. American Academy of Pediatrics Committee on Nutrition: Nutritional needs of low- birth-weight infants. Pediatrics 1985; 76: 976–986.
10. **Lucas A,** Hudson G. Preterm milk as a source of protein for low birth weight infants, Arch Dis child 1984; 59: 831-835.
11. **Kuschel CA,** Harding JE Protein supplementation of human milk for promoting growth in preterm infants (review), Cochrane data base Syst Rev 2000; 2: CD000433.
12. **Lucas A,** Moley R, Cole TJ *et al.* Early diet in preterm babies and developmental status at 18 months. Lancet 1990; 335: 1477-1482.
13. **Lucas A,** Morley R, Cole TJ *et al.* Breast milk and subsequent intelligence quotient in children born preterm. Lancet 1992; 339: 261- 266.
14. **Huppi PS.** Nutrition for the brain. Pediatr Res 2008; 63: 229 - 234.
15. **Isaacs EB,** Gadian DG, Sabatini S, *et al.* The effects of early human diet on caudate volumes and IQ. Pediatr Res 2008; 63: 308- 313.
16. **Ben X** Nutritional management of newborn infants: Practical guidelines. World J Gastroenterol 2008; 14: 6133–6139.
17. **Hay WW Jr.** Nutrition and development of the fetus: carbohydrate and lipid metabolism. In: Walker WA, Watkins JB, Duggan CP (eds): Nutrition in Pediatrics. Basic Science and Clinical Applications, ed 4. Hamilton, Decker, 2008, pp 311–325.
18. **Battaglia FC,** Meschia G. An Introduction to Fetal Physiology. Orlando, Academic Press, 1986, pp 100–135.
19. **Davies PA.** Low birth weight infants: immediate feeding re-called. Arch Dis Childhood 1991; 66:551-553.
20. Neu J. Gastrointestinal development and meeting the nutritional needs of premature infants. Am J Clin Nutr 2007; 85 (2 Suppl): 629S – 634S.
21. **Ziegler EE,** Carlson SJ. Early nutrition of very low birth weight infants. J Maternal Fetal Neonatal Med 2009; 22:191-197.
22. **Tyson JE,** Kennedy KA. Trophic feedings for parenterally fed infants. Cochrane Database Syst Rev 2005; 3: CD000504.
23. **Dunn L,** Hulman S, Weiner J, Kliegman R. Beneficial effects of early hypocaloric enteral feeding on neonatal gastrointestinal function: preliminary report of a randomized trial. J Pediatr 1988; 112: 622–629.
24. **Meetze WH,** Valentine C, McGuigan JE, *et al.* Gastrointestinal priming prior to full enteral nutrition in very low birth weight infants. J Pediatr Gastroenterol Nutr 1992; 15:163–170.
25. **Lucas A,** Bloom SR, Aynsley-Green A. Gut hormones and 'minimal enteral feeding'. Acta Paediatr Scand 1986; 75:719-23.
26. **Cho SJ.** Enteral nutrition of the preterm infant. Korean J Pediatr. 2010 Jan; 53(1):7-13.
27. **Henderson G,** Anthony MY, McGuire W. Formula milk versus maternal breast milk for feeding preterm or low birth weight infants. Cochrane Database Syst Rev 2007; 4: CD002972.
28. **Innis SM.** Human milk: maternal dietary lipids and infant development. Proc Nutr Soc 2007; 66:397-404.
29. **Klein CJ.** Nutrient requirements for preterm infant formulas. J Nutr 2002; 132:1395S–1577S.
30. **Quigley MA,** Henderson G, Anthony MY, McGuire W. Formula milk versus donor breast milk for feeding preterm low birth infants. Cochrane Database Syst Rev 2007; 4: CD002971.
31. **Dunn L,** Hulman S, Weiner J, Kliegman R. Beneficial effects of early hypocaloric enteral feeding on neonatal gastrointestinal function: preliminary report of a randomized trial. J Pediatr 1988; 112: 622–629.
32. **Meetze WH,** Valentine C, McGuigan JE, *et al.* Gastrointestinal priming prior to full enteral nutrition in very low birth weight infants. J Pediatr Gastroenterol Nutr 1992; 15:163–170.
33. **Berseth CL.** Effect of early feeding on maturation of the preterm infant's small intestine. J Pediatr. 1992; 120: 947–953.

34. **Troche B,** Harvey-Wilkes K, Engle WD. Early minimal feedings promote growth in critically ill premature infants. Biol Neonate 1995; 67: 172–81.
35. **Silvestre MA,** Morbach CA, Brans YW, Shankaran S. A prospective randomized trial comparing continuous versus intermittent feeding methods in very low birth weight neonates. J Pediatr 1996; 128: 748–752.
36. **Gray GM.** Starch digestion and absorption in nonruminants. J Nutr 1992; 122:172-7.
37. **Shulman RJ,** Feste A, Ou C. Absorption of lactose, glucose polymers, or combination in premature infants. J Pediatr 1995; 127: 626-631.
38. **Dall'Agnola A,** Beghini L. Post-discharge supplementation of vitamins and minerals for preterm neonates. Early Hum Dev 2009; 85 (1 Suppl):27S-29S.
39. **Klein CJ.** Nutrient requirements for preterm infant formulas. J Nutr 2002; 132:1395S–1577S.
40. **Koletzko B,** Goulet O, Hunt J, *et al.* Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism), Supported by the European Society of Paediatric Research (ESPR) J Pediatr Gastroenterol Nutr 2005; 41 Suppl 2:S1–S87 - 96.
41. **Acra SA,** Rollins C. Principles and guidelines for parenteral nutrition in children. Pediatr Ann 1999; 28: 113–120.
42. Health reform foundation of Nigeria. Nigerian Health Review 2006; 1–343.