Nutritional requirements and parenteral nutrition in preterm infants

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Abstract

Intrauterine growth is supported by continuous supply of nutrients from mother to the fetus throughout pregnancy therefore preterm birth causes disruption in delivery of nutrients to the fetus. In order to allow growth rate similar to that seen in utero, or avoid extra-uterine growth retardation there should be no interruption in delivery of nutrients from time of birth onwards. Extra-uterine growth retardation is associated with adverse outcomes including chronic lung disease, increased risk to infection and abnormal neurodevelopmental outcome. Provision of appropriate nutritional requirements soon after birth is critical for normal development and growth of preterm infants. Preterm infants are often not able to tolerate volumes of oral feeds that will provide adequate daily requirements for growth within the first week or two of life, therefore parenteral nutrition is often required. Understanding nutritional requirements for preterm infants who require parenteral nutrition is very important. This review discusses the nutritional requirements for preterm infants and parenteral nutrition.

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Introduction

Major developments in neonatal care such as the use of antenatal steroids, artificial ventilation including continuous positive airway pressure, and artificial surfactant therapy have resulted in improvement in the survival of preterm infants. Preterm birth, defined as being born before 37 completed weeks of gestation, is associated with major morbidities in both developed and developing countries. The major morbidities associated with preterm births include abnormal neurodevelopmental outcomes. Abnormal neurodevelopment in preterm infants has been associated with inadequate nutrition during the early postnatal period.[1,2] Furthermore and in the short term, suboptimal nutrition is also associated with adverse outcomes which include increased susceptibility to infections, greater need for mechanical ventilation and development of chronic lung disease.[3] Undernutrition during critical periods may result in reduced cell growth in different body systems including the cardiovascular system. This may result in chronic diseases, like cardiovascular disease, later on in life.[4] Early adequate nutrition in this group of infants is therefore both important and imperative.

Goals of nutrition in preterm infants

The goal of nutritional support in preterm infants is to achieve a postnatal growth rate similar to that of a normal fetus at the same postconceptual age. The American Academy of Pediatrics recommends that growth of postnatal preterm infants in both their anthropometric indices and body composition should be the same as the normal fetus of the same gestational age.[5] In utero the growth of the fetus is achieved through accretion of the new tissue and replacement of water with protein and fat. The fetus grows at a minimum rate of 15 g/kg/day during mid-trimester and down to 10 g/kg/day at term. The water content drops from about 90% at 24 weeks of gestation to about 75% at term. The lipids and protein body content increases from about 2% and 8.8% at 24 weeks to about 11% and 12% at term respectively.[6] The weight gain of 15 g/kg/day during the postnatal growth in preterm infants is often not achieved because extrauterine compared to intrauterine life requires higher energy expenditure due to intensive care environment, illnesses, inadequate nutrition and other adverse conditions.

Extrauterine growth failure which is defined as discharge weight $< 10^{th}$ percentile of expected intrauterine growth is common and has been documented to occur in 28% of preterm infants born between 23 and 34 weeks of gestation.[7] It has also been reported that the incidence of length and head circumference being $< 10^{th}$ percentile at discharge is 34% and 16% respectively.[7] Dusick et al reported that 97% and 40% of very low birth weight infants (birth weight <1 500 g) had growth failure at 36 weeks and 18-22 months post-conceptual age respectively.[8] The reason for this is that preterm infants are often not fed enough protein and energy to meet requirements for growth similar to those of the normal fetus. This interpretation is supported by the fact that appropriate nutritional support ameliorates the protein and carbohydrate deficit and improves growth of preterm infants. The risk of growth failure increases with decreasing gestational age and birth weight. Therefore, very preterm and extreme low birth weight infants will need more intensive nutritional support.

Nutritional requirements

In order to improve growth of preterm infants there should be no interruption of nutrient provision at the time of delivery. Nutrition must be provided to newborns soon after birth. The best way to provide nutrition to newborn infants is breast milk feeding. However, it may not always be possible to start feeds soon after birth and, even when such a practice is possible, oral feeds often do not provide adequate nutrition until full feeds are given, which might take seven to 10 days, if feeds are increased gradually at a rate of 20 ml/kg/day. To achieve neonatal growth rates similar to those of the normal fetus requires that early parenteral nutrition must be started soon after birth. In such cases it becomes important to know what nutrients to give and in what quantities. Major components of nutrients in preterm infants are appropriate amounts of essential nutrients via the parenteral route mainly glucose, lipids and amino acids (Table I).

Table I: Nutrient, electrolyte, calcium and phosphorus requirements in preterm infants on parenteral nutrition

Energy	110-120 kcal/kg/day
Protein	
< 30 weeks	3.5-4.0 mg/kg/day
30–36 weeks	2.5-3.5 mg/kg/day
> 36 weeks	1.5–2.5 mg/kg/day
Carbohydrates (glucose)	6-8 mg/kg/minute
Lipids	2.5–3.5 g/kg/day
Sodium	
First week of life	0-3 mmol/kg/day
Growing preterm infants	3-5 mmol/kg/day
Intermediate phase	2-3 mmol/kg/day
Potassium	
First week of life	0-2 mmol/kg/day
Growing preterm infant	2-3 mmol/kg/day
Intermediate phase	1-2 mmol/kg/day
Calcium	60–90 mg/kg/day
Phosphorus	40–70 mg/kg/day

Energy requirements

Energy is required for different cellular and organ functions. It is stored as adenosine triphosphate (ATP) which provides cellular energy when hydrolyzed to adenosine diphosphate. Preterm infants have low energy reserves due to the fact that they are born before fat and glycogen reserves have accumulated. Energy requirements depend on the stage of development, and are higher at 24 weeks compared to 38 weeks gestational age. They are affected by resting energy expenditure and growth. Resting energy expenditure is affected by sleep state and activity levels, environmental factors such as thermoregulation and demands for tissue synthesis. Synthesis of new tissue (growth and repair) requires more energy and is affected by protein and energy intake. Major increases in lean and fat mass occur during the third trimester. Resting energy expenditure appears not to vary much with gestational age, having been estimated to be 50 kcal/kg/day, on average. Estimated average energy requirements for new tissue formation in preterm infants are 4.5-4.9 kcal/g.[9,10] If the intrauterine average weight gain of 15-17 g/kg/day is to be achieved, 67-83 kcal/kg/day will be needed in addition to the resting energy expenditure. In total, this will come to 120-130 kcal/ kg/ day of total energy intake. A number of National Committees have recommended a daily energy intake of 110-130 kcal/kg/ day in healthy premature infants to allow for growth rate similar to that of the intrauterine growth rate.[11]

Carbohydrate requirements

In early gestation the brain is larger and accounts for nearly all of whole body glucose utilization rate. Glucose utilization rates are twice as high in early gestation as they are at term. Over the third trimester, other organs such as muscles, fat and bone develop and do not use glucose at the same rate as the brain resulting in less whole-body weight-specific glucose utilization. Therefore, glucose synthetic rates in preterm infants are much higher at 6-8 mg/kg/ minute compared to term infants who synthesise glucose at a rate of 3-5 mg/kg/minute. Maintaining normal glucose concentrations that match those of the normally growing fetus (more than 50 mg/dl or 2.8 mmol/l) is important for neurodevelopment.[12]

Carbohydrates are the main energy source for the neonate receiving parenteral nutrition in the form of glucose. In order to ensure that preterm infants receive adequate amounts of glucose, glucose is initially delivered at the hepatic glucose production rate of 6-8 mg/kg/minute. Glucose levels need to be monitored regularly with initiation of parenteral nutrition as preterm infants are at risk of developing hyperglycaemia. The aim is to maintain serum glucose concentrations between 2.5 and 8.0 mmol/l, to avoid hypoglycaemia and hyperglycaemia. If glucose serum levels are at these accepted levels, glucose infusion rate may be increased gradually by 0.5-1 mg/kg/minute to a maximum glucose rate of 12–13 mg/kg/ minute to assist with delivery of energy and to support growth. Insulin may be used to achieve higher glucose delivery rates to provide more energy, but this is not a recommended practice as exogenous insulin may reduce protein synthesis and thereby affect growth.[13]

Lipid requirements

Lipid is a good source of energy because of its high energy-density (1 gram of fat provides 9 kcal or 37.8 Joules of energy, compared to 1 gram of carbohydrate and protein providing about 4 kcal or 16.8 Joules each). Lipids also provide essential fatty acids which are required for brain development. Essential fatty acid deficiency can develop within the first 72 hours of life and can be avoided by giving at least 0.5-1 g/kg/day of intravenous lipids. Essential fatty acids are converted to long chain polyunsaturated fatty acid (PUFA). Docosahexaenoic acid is the main fatty acid in the brain. It accumulates in the brain mainly during the last trimester of pregnancy.[14] Infants who do not get sufficient amounts of PUFA may have delayed visual development.[15] Therefore PUFA appears to be important for brain and visual development.

Parenteral lipid emulsions also enable delivery of lipid soluble vitamins. Lipids may need to be restricted in patients with hyperbilirubinaemia approaching exchange levels because fatty

acids may displace bilirubin bound to albumin. Lipid infusion rate of 3 g/kg/day is well tolerated without adverse effects and provides the required essential fatty acids and energy levels.

Protein requirements

Proteins are essential for normal growth and development. Growth of lean body mass is particularly dependent on protein intake in organs such as the brain. Preterm infants, when fed more protein and energy, have remarkable capacity for improved growth including parts of the brain that are particularly related to cognitive function. Preterm infants given early intravenous amino acid or enteral protein feeding show evidence of enhanced growth, including head circumference growth and brain size.[16,17] Intravenous amino acids alone with or without glucose also stimulate insulin secretion which augments amino acid stimulation of protein synthesis and protein accretion.

Amino acids should be provided soon after birth in order to prevent protein breakdown and promote growth and remodeling of cells, tissues and organs at rates that mimic the growth and body composition of the healthy fetus growing in utero. In order to maintain growth similar to that seen in utero high amino acid infusion rates must be provided. Protein must be administered with energy since, in the absence of non-protein energy, protein is oxidized and is not unavailable for protein synthesis. Increasing non-protein energy intake improves nitrogen retention by enhancing amino acid utilization for protein synthesis.

The normal fetus at mid-gestation is estimated to require 4g/kg/day of protein.[6] A number of studies have reported that failure to provide dietary protein of at least 1 g/kg/day will result in protein breakdown, presenting as negative nitrogen balance.[18-22] An amount of 25-40 kcal or 105-168 Joules of non-protein energy per gram of protein intake will optimize protein deposition.[23] Therefore, a minimum of 1 g/kg/day of protein together with 30 kcal/kg/day of non-protein energy will prevent negative nitrogen balance. It is recommended that postnatal, intravenous amino acids must be administered to provide protein of 3.5–4.0 g/kg/day for infants < 30 weeks gestational age; 2.5-3.5 g/kg/day for those between 30 and 36 weeks and 1.5-2.5 g/kg/ day for infants > 36 weeks' gestational age.[24-26]

Electrolytes, minerals, and vitamins

During the first week of life electrolytes needs are relatively low because of the free water diuresis. The sodium requirements will vary from 0-3 mmol/kg/day in the first week of life. After the initial diuresis, amounts of 2-3 mmol/kg/day of sodium and potassium will be required to maintain serum levels in the normal range. During the growing phase, the sodium requirements may double up to 4-6 mmol/kg/day.

Calcium, magnesium and phosphorus are essential for tissue structure and function. During pregnancy the fetus obtains its calcium from the mother through active calcium transfer and this reaches a peak of 120-150 mg/kg of fetal weight per day during the last trimester. Therefore preterm infants born before the last trimester are at an increased risk of low bone mass and metabolic bone disease. It has been calculated that in the last trimester the daily accretion of calcium, phosphorus and magnesium are 120, 70 and 3 mg/kg/day respectively.[27] Providing calcium and phosphorus through parenteral nutrition is a challenge because of limited solubility. It has been recommended that parenteral nutrition should contain 12.5-15 mmol/l of elemental calcium and 13-15 mmol/l of phosphorus. At parenteral nutrition fluid intake of 150 ml/kg/day, this will provide 75–90 mg/kg/day of calcium and 60–70 mg/kg/day of phosphorus. A calcium to phosphorus ratio of 1.7:1 to 1.3:1 by weight has been recommended but it appears that 1.7:1 is the optimal ratio for bone mineralization.[28] Higher early calcium (75 mg/kg/day) and phosphorus (44 mg/kg/day) intake delivered by parenteral nutrition appear to be tolerated and prevent bone strength decline in preterm infants in the first week of life.[29]

Vitamins are essential for growth and development. The infant requires both water- and fat-soluble vitamins. Water soluble vitamins need to be supplied regularly because they are not stored in significant amounts in the body. They should be administered as soon as parenteral nutrition is started. Preterm infants have low body stores of fat soluble vitamins at birth due to limited transfer of lipid-soluble substrate across the placenta. Therefore, provision of the latter should be started as soon as lipid containing parenteral nutrition is initiated. The actual vitamin requirements in preterm infants are not well determined.

Complications

Complications due to parenteral nutrition may be categorised into four groups: central venous line related, mainly sepsis and thromboembolism; deficiency or excess of parenteral nutrition components namely, electrolytes, glucose, vitamins and minerals; liver abnormalities e.g. raised enzymes, cholestasis; and metabolic bone disease and growth impairment.

Infection is probably the most serious complication associated with both peripheral and central intravenous catheters. The most commonly associated organisms are coagulase-negative *Staphylococcus, Staphylococcus aureus* and *Candida* species.[30,31] Peripheral lines may infiltrate within a short period and such tissue damage increases the risk of infection. Peripheral lines may become colonized at a rate of 30%, if they have been in place for more than three days.[30] Central venous catheters can also be infected but have the advantage of lower risk of infiltration.

Hyperglycaemia is a common problem in preterm infants on parenteral nutrition. The most common cause is high glucose infusion. Preterm infants who require parenteral nutrition are often ill with thermal instability, hypotensive in need of inotrope support and septic. In such infants, stress hormones such as catecholamines are released and inhibit insulin secretion and action, and promote glycogen breakdown leading to hyperglycaemia. Intravenous lipid infusion also contributes to hyperglycaemia by competitively limiting glucose oxidation and promoting gluconeogenesis.[32] Treatment of hyperglycaemia might require that the glucose delivery is reduced

to 4 mg/kg/minute or less and limiting intravenous lipid infusion. Early use of amino acids in parenteral nutrition may reduce the risk of hyperglycaemia as amino acids may promote insulin secretion which will diminish hepatic glucose production and enhance glucose utilization. If hyperglycaemia, persists despite reducing glucose delivery rate, insulin infusion should be considered.

There has been reluctance to provide early and high protein parenteral nutrition because of fear of potential amino acid toxicity, uremia and metabolic acidosis. These complications were seen more frequently during the earlier days of parenteral nutrition support when solutions that were being used were unbalanced with a relatively low essential amino acids content and a high in non-essential, potentially, toxic amino acid. Urea production is normally high when there are high rates of amino acid oxidation, which increase urea synthesis. This urea production can be avoided by minimizing amino acid oxidation and by providing adequate non-protein energy sources. A study by Ridout et al showed that there was no correlation between intravenous amino acid intake and urea oxidation in preterm infants, including the extremely low birth weight infants.[33] A number of studies have not shown metabolic acidosis to be common in preterm infants fed relatively higher rates of amino acids.[20,21,34]

Metabolic bone diseases associated with parenteral nutrition are related to abnormalities in calcium and phosphorus levels, and excess aluminium contamination.[35] The pathogenesis of TPN associated liver diseases is not well understood. The initial pathology is usual cholestasis, followed by portal inflammation and bile duct proliferation. With prolonged use of TPN portal fibrosis and cirrhosis may develop. The cause of cholestasis is thought to be multifactorial and includes sepsis, lack of enteral nutrition, and quantity and composition of parenteral amino acids.

Benefits of early aggressive nutrition in preterm infants

The change from a well-parenterally fed state in utero to the extrauterine life with different metabolic demands or physiological properties is a major challenge to the preterm born infant. If the preterm infant does not receive parenteral nutrition or full enteral feeding directly after birth, the infant will become catabolic with nitrogen losses. It is estimated that 1% of the endogenous body protein will be lost per day, if the preterm infant is provided with only glucose after birth.[8,36] Therefore, there is an urgent need for optimal nutrition at the time of birth.

In the past there has been reluctance to start parenteral nutrition soon after birth because of fear of hyperglycaemia, metabolic acidosis, and uraemia. However, early parenteral nutrition has been shown to reduce hyperglycaemia due to amino acids stimulating the release of insulin, thereby promoting glucose utilization. Metabolic acidosis and uraemia have not been found to be specific to parenteral nutrition (amino acids) but rather to be influenced by the general clinical condition of the infant.[36-38]

It has been shown that increasing protein and energy intake within the first 24 hours after birth is associated with higher Mental Development Index scores.[39] Starting parenteral nutrition on day one reduces the incidence of growth failure seen at 36 weeks postnatal age. Early lipid administration by day two of life is well tolerated.[40] Therefore, recommendations have been made that at least 1.5 g/kg/day of protein should be started within the first 24 hours of life and then increased by 0.5-1 g/kg/day to 3.5-4.0 g/kg/day. Lipids should be provided between 24 and 48 hours of life at 0.5-1.0 g/kg/day and increased by 0.5-1.0 g/kg/day to 3.0-3.5 g/kg/day. A number of studies have reported on an aggressive approach of starting parenteral nutrition that provides protein $\geq$ 1.5 g/kg/day within the first 24 hours of life and lipids at 0.5-1.0 g/kg/day on day two.[18,19,22] These studies reported that early high protein and early lipid intake resulted in increased nitrogen balance and energy, without metabolic acidosis, or high levels of urea, cholesterol and triglycerides.

Prepacked bags of parenteral nutrition should be available in the neonatal unit at all times to facilitate early commencement of nutrition soon after birth. Amino acids should be started within the first 24 hours of life at not less than 1.5 g/kg/ day. If the prepacked bags of TPN that are lipid free are not available then the TPN should be started on day 2 to provide protein at 1.0-1.5 g/kg/day.

Monitoring infants on TPN

Complications of parenteral nutrition can be related to lack or excess of electrolytes, minerals and nutrients in parenteral nutrition, therefore these should be monitored for. The suggested monitoring schedule and the parameters to be monitored for infants who are on parenteral nutrition are shown on Table II.

Table II: Parameters to be monitored on infants on parenteral nutrition

Test/ Measurement	Frequency
Glucose (haemoglucotest)	Six to eight hourly while increasing glucose infusion rate Once to twice a day once on stable glucose infusion
Serum electrolytes and urea	Twice a week while increasing fluid rate, then weekly
Serum calcium, magnesium and phosphorus	Weekly
Liver function tests	Weekly
Serum triglycerides	Weekly
Urine glucose	Same time as glucose or each urine
Weight, length and head circumference	Weekly

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