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PRINCIPLES AND PRACTICE OF PARENTERAL NUTRITION IN THE NEONATAL PERIOD

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SUMMARY

In extremely preterm or critically-ill infants, the parenteral route for maintaining nutritional integrity has to be relied upon before successful transition to the enteral route of feeding is achieved. Parenteral nutrition is now a fundamental part of neonatal intensive care. Fluid intake volumes vary from 60-150 ml/kg/d, depending on maturity of the infant and environmental conditions influencing insensible water loss from the skin. Parenteral nitrogen requirements are 30-35 mmol/kg/d, equivalent to 3.0-3.5 mg/kg/d of amino acids. Hyperglycaemia during parenteral nutrition can be minimised by starting glucose infusion at a rate of 6-8 g/kg/d with progressive increase to 18-20 g/kg/d by 2-3 weeks after birth. Parenteral fat is introduced at 1 g/kg/d, gradually increasing to 3 g/kg/d, given as a continuous infusion. An energy intake of 50 kcal/kg/d is adequate to match ongoing expenditure but an additional energy intake of 70 kcal/kg/d is required to achieve optimal growth. Minerals and trace elements delivered with parenteral nutrition are calculated to meet in-utero accretion rates. Multivitamins available for parenteral use should also be included. Improved techniques for the preparation, administration and monitoring of parenteral nutrition have helped minimise catheter-related and metabolic complications. In neonatal intensive care units where appropriate medical, nursing, pharmacy and laboratory expertise are available, the potential benefits of parenteral nutrition outweigh its hazards. Nevertheless, early initiation of enteral feeding in small subnutritional quantities to supplement parenteral nutrition is of major importance to enhance the growth and development of the gastrointestinal tract.

RESUMO

Princípios e Prática de Nutrição Parenteral no Período Neonatal

Nos grandes pretermos e em recém-nascidos gravemente doentes, a nutrição parentérica é necessária para manter a integridade nutricional, até se conseguir a transição para a via entérica. A nutrição parentérica é hoje fundamental nos cuidados intensivos. O aporte hídrico varia entre 60 a 150 ml/kg/dia, de acordo com a maturidade e as condições ambientais que influenciam a perda insensível de água pela pele. Quanto ao nitrogénio, são necessários 30-35 mmol/kg/d, equivalentes a 3.0-3.5 mg/kg/d de aminoácidos. A hiperglicemia pode ser minimizada iniciando perfusão de glucose num ritmo de 6-8 g/kg/d com aumento progressivo até 18-20 mg/kg/d pelas 2-3 semanas após o nascimento. Os lípidos são introduzidos a 1 mg/kg/d, com aumento gradual até 3 g/kg/d, em perfusão contínua. O aporte calórico de 50 kcal/kg/d é adequado para obviar o catabolismo proteico mas deve ser superior a 70 kcal/kg/d para o crescimento. As necessidades em minerais baseiam-se nos índices verificados para o crescimento fetal intra-uterino. Também devem ser incluídas as multivitaminas existentes para uso parentérico. As técnicas desenvolvidas para a preparação, administração e controlo da nutrição parentérica têm ajudado a minimizar as complicações de ordem metabólica. Os benefícios potenciais da nutrição parentérica são maiores que os riscos em unidades de cuidados intensivos neonatais com o devido profissionalismo médico, de enfermagem, farmacêutico e laboratorial. No entanto, o início precoce da nutrição entérica em pequenas quantidades subnutricionais é de grande importância para acentuar o crescimento e desenvolvimento do tracto gastrointestinal.

INTRODUCTION

The fetus is nourished parenterally during pregnancy through the regulatory function of the placenta but after birth, extrauterine adaptation depends on successful transition to the enteral route of nutrition. It is a major challenge to provide optimal nutrition for infants compromised by major clinical problems or developmental immaturity after birth. The parenteral route for maintaining nutritional integrity postnatally has been developed for infants whose gastrointestinal function is compromised and for whom adequate nutrition cannot be provided enterally. Parenteral nutrition has now evolved to become a fundamental part of the intensive care support for critically-ill or preterm infants. A 1983 survey of 269 American neonatal intensive care units showed that 80% of units used parenteral nutrition in the first week for extremely low birthweight (ELBW, <1000g) infants.[1] It is the purpose of this review to describe the principles and practice of parenteral nutrition in these high-risk infants.

INDICATIONS

Parenteral nutrition is indicated in the infant for whom feeding via the enteral route is impossible, inadequate or hazardous, because of malformation, disease or immaturity, and in whom this state is likely to be prolonged and pose a serious threat to life and health. It is used in infants with major anomalies such as intestinal atresia or omphalocele, necrotising enterocolitis (NEC) or protracted diarrhoea from a variety of causes. They may have had extensive intestinal resection or require multiple surgical procedures. In some, resting the gastrointestinal tract for a prolonged period is curative. In others, maintenance of adequate nutrition will permit corrective surgery to be carried out. Parenteral nutrition is also used in extremely preterm infants, especially those with respiratory distress, prior to enteral feeding or to supplement milk feeds which can then be increased slowly to avoid overtaxing the immature gastrointestinal tract while continuing to satisfy nutritional requirements. In any clinical situation however, parenteral nutrition is only justified if the benefits outweigh the hazards. As the safety of the technique depends on available resources and expertise, indications for parenteral nutrition necessarily vary between centres. If facilities for intensive medical and nursing care and frequent biochemical monitoring using microtechniques are unavailable, it seems wiser to transfer the infant to an appropriate centre for parenteral nutrition.

FLUID INTAKE

The extracellular fluid (ECF) volume is high in preterm infants compared to term infants and there is a normal reduction in ECF after birth which accounts for their postnatal weight loss.[2] A randomised controlled trial (RCT) was carried out in infants with a birthweight of 750-1500g to compare two parenteral fluid regimens: one which allowed 1-2% loss of birthweight per day to a maximum loss of 8-10% versus one which allowed 3-5% loss per day to a maximum of 13-15%.[3] No difference in neonatal mortality and morbidity was found between the two groups, suggesting that the gradual loss of 15% of birthweight in the first week after birth is safe. It has been shown that although the mean postnatal weight loss in infants born at 26-29 weeks gestation was 12-15% of birthweight, although those born at 25 weeks or less had a mean loss of about 20%.[4] This can be explained by an increased and uncompensated transepidermal water loss secondary to an underdeveloped stratum corneum before cornification occurs.[5] Both gestational age and postnatal age have a profound effect on transepidermal water loss.[6]

Insensible water loss (IWL) in preterm infants ranges from 50 ml/kg/d to over 150 ml/kg/d depending on environmental factors. A 40-60% increase in IWL has been reported with the use of radiant warmers and/or phototherapy,[7] an increase of 1-2°C in ambient temperature,[8] nursing under conditions of forced convection,[9] and parenteral nutrition.[10] IWL can be doubled in the most extreme situation. Measures which are effective in reducing IWL by 30-60% in infants nursed in incubators or under radiant warmers include the use of perspex heat shields,[11,12] plastic blankets[12,13] and a high ambient humidity.[14] If preterm infants are nursed in maximally humidified incubators, their fluid requirement is similar to that of larger infants: 60-80 ml/kg/d increasing to 100-120 ml/kg/d over the first week.[3] When the ambient humidity is approximately 50%, the recommendation is to start at 100 ml/kg/d increasing to 150 ml/kg/d.[15] If measures to reduce IWL are not taken, fluid requirements for some ELBW infants will increase to 200 ml/kg/d. Serial assessment of hydration status is mandatory, using clinical and laboratory parameters.

ENERGY

The initial goal of parenteral nutrition is to infuse adequate energy and nitrogen to prevent catabolism and achieve positive nitrogen balance. Preterm infants have low energy reserves due to diminished glycogen stores in the liver and reduced fat deposits. Fortunately, they also have a near-fetal basal metabolic rate as low as 30 kcal/kg/d if nursed in a thermoneutral environment with minimal activity. However, cold stress which reduces abdominal skin temperature by 1°C will produce a 10-15% increase in energy expenditure.[16] Furthermore, the energy cost of physical activity is about 4 kcal/kg/d even with minimal handling.[17] A parenteral input of about 50 kcal/kg/d is sufficient to match ongoing expenditure but it does not meet additional requirements of growth.[18] It has been shown that with this energy intake, postnatal weight loss remained <5% of birthweight and, although contraction of the extracellular compartment did occur, an expansion of the intracellular compartment was demonstrated which might be related to the onset of growth.[2]

The energy cost of growth is about 5 kcal/g of tissue increment.[17] It includes the extra energy expended for the

actual synthesis of tissue, which is thought to represent the specific dynamic action of food. This value for parenteral nutrition approximates 13% of basal metabolic rate or 10% of the energy infused.[19] Theoretically, to achieve the equivalent of third trimester intrauterine weight gain of 14 g/kg/d, an additional energy intake of about 70 kcal/kg/d is required. However, studies have shown that growth rates and nitrogen accretion similar to in utero values can be sustained by parenteral nutrition with an intake of 80 kcal/kg/d when an appropriate amount of nitrogen is infused.[20,21] Parenterally fed infants, compared to those enterally fed, begin to grow at a lower energy intake because of smaller faecal energy losses and reduced energy expenditure. Nevertheless, the goal energy intake for a rapidly growing preterm infant is theoretically about 120 kcal/kg/d. This value will even be higher in long-term ventilated infants with chronic lung disease (CLD) whose energy requirements are increased by 25-30%.[22]

GLUCOSE

With few exceptions, ELBW infants require parenteral glucose for maintenance of euglycaemia during the first few days after birth. Data from brainstem auditory and somatosensory evoked potential testing[23] and neurodevelopmental outcome[24] suggest that the blood glucose concentration should be maintained above 2.6 mmol/l irrespective of the presence or absence of abnormal clinical signs. The provision of parenteral glucose during the first 2 days after birth has been shown to reduce endogenous protein catabolism of preterm infants by about 80%.[25] Unfortunately, the risk for hyperglycaemia and glucosuria increases with decreasing gestation and birthweight[26,27] and in those under stress from hyaline membrane disease.[28] Hyperglycaemia during glucose infusion appears to be due to persistent endogenous hepatic glucose production secondary to an insensitivity of hepatocytes to insulin.[29,30]

In ELBW infants in whom parenteral fluids are commenced at 60-80 ml/kg/d, 10% dextrose can be used which provide a glucose infusion rate of 6-8 g/kg/d (4-6 mg/kg/min). If a fluid intake of over 80 ml/kg/d is prescribed, it is advisable to use 5% dextrose in order not to exceed the above glucose infusion rate in the first days after birth. Glucose tolerance improves with increasing postnatal age.[31] Under careful monitoring of blood glucose during infusion, the glucose infusion rate can be safely increased progressively to 18-20 g/kg/d (12-14 mg/kg/min) in the second or third week. It is necessary to limit the concentration of the dextrose solution infused into peripheral veins to about 12% because of the risks of subcutaneous tissue infiltration. Therefore, the higher glucose infusion rates require central venous access.

Hyperglycaemia has been defined as a serum glucose of over 8 mmol/l[27] at which level glycosuria often develops.[26] The untoward effects of osmotic diuresis are however uncommon in preterm infants with glycosuria.[26,29] Nevertheless, it is prudent to maintain a serum glucose below the level mentioned above in view of the fact that it is uncertain when the brain metabolism is compromised and the risk of intracranial haemorrhage is increased. The appropriate response to hyperglycaemia is to reduce the glucose infusion rate. Insulin therapy has been used successfully in those infants who remained hyperglycaemic at a glucose infusion rate of 8 g/kg/d (6 mg/kg/min).[32] A continuous insulin infusion, starting at 0.05 units/kg/hr, has been recommended.[33] A RCT of insulin therapy in ELBW infants with glucose intolerance has been shown to improve glucose intake and weight gain.[34]

NITROGEN

It has been customary practice for parenteral amino acids to be introduced when the energy intake from glucose exceeds 50 kcal/kg/d, equivalent to a glucose infusion rate of 12 g/kg/d (9 mg/kg/min). With lower energy intakes, more of the infused amino acids are oxidized to meet endogenous energy needs and less for tissue synthesis. In a RCT among extremely preterm infants, a negative nitrogen balance of about 10 mmol/kg/d equivalent to a daily loss of 3% of the body's protein has been found in the first 3 days after birth before amino acids were commenced.[35] Infants who received 1.5-1.8 g/kg/d amino acids within the first day of birth while receiving an energy intake of 45 kcal/kg/d had a nitrogen retention rate of 9 mmol/kg/d and increased protein synthesis.[35,36] This early introduction of parenteral amino acids which permits positive nitrogen balance is well tolerated and does not elevate plasma amino acid levels even in sick preterm infants.[37]

The intrauterine nitrogen accretion rate for a fetus is constant at 24 mmol/kg/d between 24 and 36 weeks of gestation.[38] The parenteral nitrogen required to achieve retention equal to the fetal accretion rate depends on a number of factors such as energy intake, the quality of infused amino acids, vitamin and mineral co-factors, and the patient's clinical status. Crystalline amino acids have replaced protein hydrolysates as the nitrogen source in parenteral nutrition as they have a higher bioavailability. Furthermore, amino acids in the form of L-stereoisomers are preferred due to the excessive urinary loss of metabolically inactive D-stereoisomers. Nitrogen retention of over 70% of the amount infused was found for amino acid formulations such as Vamin[21] and Trophamine.[39] Using such solutions, a parenteral nitrogen intake of 32 mmol/kg/d can result in duplication of intrauterine nitrogen accretion rates. This is equivalent to 3.3 g/kg/d of amino acids. It has been shown in two RCTs that a parenteral intake of 4 g/kg/d compared to 2-3 g/kg/d resulted in higher nitrogen retention, net protein synthesis and weight gain.[20,40] As nitrogen retention has been shown to be reduced by more than 50% during dexamethasone therapy for CLD, it may be appropriate to provide additional amino acid intake during the treatment period.[41,42]

The preterm infant not only requires more amino acids than term infants but also qualitatively different amino acids. Cysteine, taurine, tyrosine and histidine have been considered as conditionally essential amino acids in

preterm infants.[43] Conversion of methionine to cysteine and taurine and conversion of phenyalanine to tyrosine are affected by enzyme immaturity. The optimal composition of an amino acid solution for ELBW infants is uncertain. The reference standard against which to assess the plasma aminogram in such infants remains controversial. Comparison of amino acid solutions based on the composition of egg protein[44] and breast milk[45] has shown that the latter results in a lower risk of high plasma phenylalanine levels but a higher risk of low tyrosine levels.[46,47] However, no adverse neurodevelopmental outcome had been observed after hyperphenylalaninaemia induced by parenteral nutrition.[48] Amino acid solutions designed for paediatric patients have been shown to result in a more favourable plasma aminogram, higher nitrogen retention and better weight gain in preterm infants.[49,50] Cysteine[51] and taurine[52] have been added to some amino acid solutions, as they are considered to be essential in preterm infants. Amino acid solutions have been designed using the engineering technique of optimisation, in which the composition is derived from calculations based on a large body of plasma amino acid data from patients who have received a variety of parenteral amino acid solutions. Studies have shown that preterm infants tolerate well these 'designer' amino acid solutions.[53] The metabolic capacity of preterm infants for parenterally delivered amino acids is not as limited as commonly thought and in general, their plasma aminograms are comparable to those found in term infants fed on human milk.[54,55]

FAT

Parenteral fat is used in parenteral nutrition as a major nonprotein energy source. Similar nitrogen sparing effects have been documented for glucose and fat in parenterally-fed infants under steady-state conditions.[56,57] Parenteral fat also prevents essential fatty acid deficiency. Both soybean (Intralipid) and safflower (Liposyn) emulsions are well tolerated. Essential fatty acid deficiency can be prevented by as little as 0.5 g/kg/d of Intralipid[58] and 0.3 g/kg/d of Liposyn.[59] The optimal ratio of linoleic and linolenic acid is thought to lie between that in the two oil emulsions.[60] Parenteral fat preparations which contain medium-chain triglycerides have been shown to be well tolerated by infants[61] and result in a lower serum cholesterol[62] and greater nitrogen retention[63] compared to those which are composed of long-chain triglycerides of soybean or safflower origin.

Parenteral fat tolerance is poor in preterm compared to term infants[64] especially in those who are ELBW.[65] This is probably due more to deficient cellular uptake and utilisation of free fatty acids than low lipoprotein lipase activity.[66] Carnitine is essential for optimal fatty acid oxidation because it facilitates their transport across the mitochondrial membrane. Preterm infants develop low blood and tissue carnitine levels on parenteral nutrition using carnitine-free solutions because they are born with low carnitine depots and have limited capacity for carnitine biosynthesis.[67-69] Although the effect of carnitine supplementation was inconsistent in previous short term studies,[70-73] it has been shown to improve fat utilisation in infants on prolonged parenteral nutrition.[74] Carnitine supplementation is therefore recommended in those who have been on total parenteral nutrition for longer than four weeks.[75]

Although it has been suggested that parenteral fat should be withheld in the first week after birth as early use of fat infusion might be associated with respiratory compromise, RCTs have shown that it was well tolerated even if commenced on the day of birth with no increase in adverse effects, including CLD.[76-78] However, free radicals generated when Intralipid undergoes peroxidation could be potentially damaging to preterm infants.[79] Phototherapy-induced formation of triglyceride hydroperoxides can be prevented by covering the Intralipid with aluminium foil.[80] Parenteral fat should be commenced in a dose not exceeding 1 g/kg/d increasing within a week to 3 g/kg/d,[81,82] although this should be reduced to 2 g/kg/d in preterm infants during acute sepsis because of their reduced fat oxidation rate.[83] Compared to 10% Intralipid, 20% Intralipid has a lower phospholipid/triglyceride ratio and liposomal content, and RCTs have shown that the 20% emulsion resulted in lower plasma triglyceride, cholesterol and phospholipid concentrations.[84,85] Two RCTs have shown that a continuous fat infusion regimen is better than an intermittent regimen, as reflected by less fluctuation in serum levels and a lower incidence of clinical and metabolic complications.[86,87] Plasma turbidity assessed by visual inspection or nephelometry does not reliably predict serum concentration.[88] When triglyceride levels exceed 1.7 mmol/l, it is necessary to reduce or interrupt fat infusion until normal values are regained.[89,90]

Table 1 – Recommendations for intravenous minerals and trace elements in preterm infants (amount per kg per day)

Sodium	3-5 mmol	(70-120 mg)
Chloride	3-5 mmol	(110-180 mg)
Potassium	1-2 mmol	(40-80 mg)
Calcium*	1.5-2.2 mmol	(60-90 mg)
Phosphorus*	1.5-2.2 mmol	(50-70 mg)
Magnesium	0.3-0.4 mmol	(7-10 mg)
Zinc	6-8 umol	(400-500 ug)
Copper	0.3-0.6 umol	(20-40 ug)
Selenium	13-25 nmol	(1-2 ug)
Manganese	18-180 nmol	(1-10 ug)
Iodine	8 nmol	(1 ug)
Chromium	4-8 nmol	(0.2-0.4 ug)
Molybdenum	2-10 nmol	(0.2-1 ug)

* Based on an 120-150 ml/kg/d fluid intake of a solution which contains 1.3-1.5 mmol/dl of calcium and phosphorus (molar ratio 1:1) equivalent to 50-60 mg/dl of calcium and 40-45 mg/dl of phosphorus (weight ratio 1.3:1)

MINERALS AND TRACE ELEMENTS

In the first week after birth, hypernatraemia in preterm infants is due primarily to their high IWL and hyponatraemia to inappropriate arginine vasopressin release associated with periventricular haemorrhage, pneumothorax or hyaline membrane disease.[91] The same study

suggested that 1 mmol/kg/d of sodium is sufficent in the first week before diuresis sets in. However, late hyponatraemia is due to limited tubular sodium reabsorption[92] which results in some preterm infants requiring a sodium intake of over 5 mmol/kg/d, especially those who are receiving frusemide for CLD. Although a potassium intake of 1-2 mmol/kg/d is required for the rapidly growing preterm infant, potassium should be withheld in the first three days after birth in ELBW infants who are at risk of developing nonoliguric hyperkalaemia due to immature distal tubular function.[93,94] Hypochloraemic alkalosis is prevented by a chloride intake of 2 mmol/kg/d. However, a total chloride load in excess of 6 mmol/kg/d is inadvisable in preterm infants as it is associated with an increased risk of hyperchloraemic metabolic acidosis.[95]

Because of the normal decrease and spontaneous increase of serum calcium in the first week after birth in preterm infants, hypocalcaemia is defined as less than 1.7 mmol/l, a value lower than that used in term infants. The parenteral administration of calcium at 1 mmol/kg/d from birth can prevent early neonatal hypocalcaemia in preterm infants without depressing their parathyroid activity.[96] The relationship between ionised and total calcium may not be constant. The parenteral requirements for calcium and other minerals, calculated to match intrauterine accretion rates in a rapidly growing preterm infant, are however higher than that used to maintain short-term homeostasis. RCTs have shown that it is possible to provide calcium and phosphorus intakes close to that of intrauterine accretion rates and that these higher intakes benefit the infant's homeostasis mechanisms with greater retention of these minerals and greater bone mineral content.[97-99] *Table 1* summarises the recommendations on parenteral minerals and trace elements for preterm infants based on guidelines published by the American Society for Clinical Nutrition.[100] Parenteral nutrition solutions should contain 1 3-1.5 mmol/dl calcium and phosphorus (molar ratio of 1:1 or a ratio of 1.3:1 by weight) administered with a fluid intake of 120-150 ml/kg/d. These recommendations are described per unit volume to prevent administration of high concentrations of calcium and phosphorus resulting in precipitation of these minerals when fluid intake is restricted.

Except for zinc, no trace elements need to be added in the first two weeks of total parenteral nutrition or when parenteral nutrition is administered as a supplement to enteral feeding.[100] The risk of zinc deficiency is increased with excessive gastrointestinal fluid losses, as is the risk of copper deficiency when there are losses of copper-containing biliary secretion. Copper and manganese supplements should be withheld in the presence of cholestasis, and selenium and chromium supplements withheld when renal function is impaired. Since destruction of erythrocytes postnatally provides the infant with 18 umol/kg/d of iron, iron supplementation is unnecessary, especially if the infant is receiving repeated top-up transfusions. Molybdenum and fluoride supplements should be considered only with long-term total parenteral nutrition exceeding six months. The aluminium content of parenteral nutrition infusates may be up to 1 µmol/dl as a result of aluminium contamination of the components used, such as calcium gluconate, which can contribute to 80% of the total aluminium load. Although the consequences of aluminium accumulation and bone deposition in infants on parenteral nutrition are unclear, it is advisable to minimise aluminium contamination in infusates.[101]

VITAMINS

Compared to term infants, those born preterm have a lower level of adaptation to parenteral vitamins and an increased potential for deficiency or toxicity. An appropriate formulation needs to be developed for preterm infants. In the meantime, MVI-Paediatric in the dose of 2 ml/kg/d up to a maximum of 5 ml/d, is considered to best suit the preterm infant's requirements, even though low levels of vitamin A and high levels of most of the B vitamins has been reported with its use.[100] About 80% of vitamin A and 30% of vitamins D and E are lost during administration due to adherence to tubing and photodegradation, especially during phototherapy.[102,103] By adding the vitamin preparation into the fat emulsion instead of the amino acid-glucose mixture, vitamin A loss can be reduced to 10% and the risk of deficiency minimised.[104,105]

PRACTICAL CONSIDERATIONS

Preparation. Computer programs are available which improve the efficiency of prescribing parenteral nutrition, reduce human error with automatic physiological safety and precipitation checks, and increase the ease of nutritional data retrieval.[106-112] All preparations should be carried out under strict aseptic conditions using a laminar flow hood and terminal filtration with a 0.22 µm filter prior to delivery to the neonatal unit. A RCT has shown that a centralised system of managing parenteral nutrition with pharmacist monitoring resulted in higher nutrient intake, better weight gain and fewer complications.

Delivery. An infusion pump is required to maintain a constant rate of delivering the parenteral nutrition solution. A 0.22-µm bacterial filter is commonly used if terminal filtration is not carried out in the pharmacy. Distal to the filter, a second infusion pump delivers the fat emulsion close to the intravascular catheter. It is important to minimise mixing of the fat emulsion with calcium and heparin as this increases the risks of formation of calcium-phosphorus crystals and flocculation of Intralipid due to the destabilising effect of divalent cations.[113] If peripheral veins are used, studies in preterm infants have shown that short catheters remain functional significantly longer than steel needles with no increase in complications.[114,115] As the nutrient mixture infused into a peripheral vein cannot be as concentrated as that infused into a central vein, central venous catheterisation is necessary if parenteral nutrition is required for a long

period of time. When central venous catheters are used, the distal tip of the catheter is placed in the superior or inferior vena cava near the right atrium. Favourable experience has been reported on percutaneous central venous catheterisation in ELBW infants,[117-119] a technique which is preferred to the surgical cutdown approach.[120] The Broviac catheter developed for long-term parenteral nutrition has also been used successfully in ELBW infants.[121,122] Recent advances in catheter technology have enabled the use of prolonged parenteral nutrition with relatively few technical complications. The addition of heparin (1 unit/ml) to the infusate further reduces significantly the incidence of phlebitis and thrombosis of both peripheral[123] and central venous catheters.[124,125] Infusion of lipid emulsions can also prolong survival times of peripheral venous lines.[126] Parenteral nutrition has been administered routinely through umbilical arterial catheters in infants who require arterial access for blood gas monitoring in the first two weeks of age.[127] This has been found to be comparable to central venous catheters in efficacy and safety.[128] The umbilical venous catheter has also been compared favourably with the use of peripheral veins in delivering parenteral nutrition.[129]

Monitoring. Daily body weight and weekly body length and head circumference measurements should be carried out. In the initial period when parenteral nutrients are being graded up or during any period of metabolic instability, strict fluid balance, 6-12 hourly urine and blood glucose, and daily plasma sodium, potassium, calcium, urea and acid-base determinations are required. When the infant is on full parenteral nutrition and is in a metabolic steady state, there investigations are carried out once or twice weekly. In addition, measurements of plasma magnesium, phosphorus, alkaline phosphatase, albumin, transaminases and bilirubin are recommended weekly. Plasma triglycerides, amino acids, trace elements and ammonia are usually not routinely monitored. Screening for infection or coagulation defects is carried out as indicated. Investigations should be performed with discretion and a compromise must be made between the need for laboratory information and the risks and cost of repeated tests. As many preterm or postoperative infants requiring parenteral nutrition have metabolic problems associated with their primary condition, it is no easier to generalise on the frequency of laboratory monitoring than it is on the frequency of clinical examinations.

BENEFITS

RCTs have shown that infants on total[127,130] and supplemental[131-135] parenteral nutrition had less postnatal weight loss, more rapid weight gain and an earlier age when the birthweight was regained compared with those fed conventionally.[113-118] This weight gain associated with parenteral nutrition has been shown to result from tissue accretion rather than water retention.[136,137] Weight gain consistently above intrauterine growth rate can be achieved after two weeks of age for those born at 29 weeks of gestation, after three weeks of age at 26-28 weeks and after four weeks of age at 24-25 weeks.[4] The improved early growth pattern was reported to be associated with a lower incidence of growth failure in late infancy.[138] In addition to its nutritional benefits, parenteral nutrition can potentially contribute to a reduction in morbidity and mortality from specific diseases. Enteral feeding in preterm infants increases the risk of aspiration pneumonia, cardiorespiratory disturbances and NEC.[139-143] Parenteral nutrition allows the cautious and gradual introduction of enteral feeding, thus minimising these risks. A meta-analysis of the two RCTs of total parenteral nutrition[127,130] showed that the incidence of NEC was significantly reduced with parenteral nutrition.[144] Sick, preterm infants on prolonged assisted ventilation were found to tolerate their initial enteral feeds better and have a shorter convalescent period when given parenteral nutrition.[145]

HAZARDS

Infection and technical complications. Infants on parenteral nutrition have an increased risk of bacterial sepsis caused by staphylococcus epidermidis and aureus[146] and fungal sepsis.[147,148] The prevalence of catheter-related sepsis ranges from 8% to 45%, with staff training playing a key role in its prevention.[149] To minimise the risk of sepsis, the following precautions should be taken: (1) Preparation of individual aliquots of parenteral nutrition solutions in the pharmacy as previously described is encouraged. (2) Manipulations carried out in the ward increase the risk of polymicrobial bacteraemia and should be avoided.[150,151] (3) Silastic catheters rather than polyethylene or polyvinyl catheters should be used and they must be placed under strict aseptic conditions. (4) The skin exit site for the catheter should be placed in an area which can be meticulously cleansed. (5) Proper care of the site and all the connectors and tubings is essential. (6) The addition of heparin (1 u/ml) to the infusate reduces infection of peripheral and central venous catheters as described previously. Uncommon but serious complications of central venous catheterisation include superior or inferior vena cava obstruction, cardiac arrhythmia or tamponade, intracardiac thrombi, pleural effusion or chylothorax, pulmonary embolism, Budd-Chiari syndrome, and hydrocephalus secondary to jugular vein thrombosis. Though these problems can be avoided with peripheral vein infusion, frequent insertions of peripheral venous catheters results in excessive handling of the infant. Extravasation of the infusate can lead to serious tissue necrosis and subcutaneous calcium deposition.

Metabolic complications. The risks of abnormal plasma aminograms, hyperammonaemia, hyperchloraemic metabolic acidosis, and mineral and trace element deficiencies, are minimised with the careful choice of amino acid solutions and appropriate additives to the infusate. It has been shown that an arginine intake of at least 0.5 mmol/kg/d is required to prevent hyperammonaemia.[152] As septic infants are at risk for hyperammonaemia during parenteral nutrition,[153] their amino acid intake

should be temporarily reduced or ceased when sepsis is first diagnosed.

RCTs which have established the safety of early introduction of parenteral fat in infants were referred to previously. In addition, short-term studies have shown no detrimental effect on oxygenation or pulmonary haemodynamics in preterm infants with severe respiratory distress syndrome unless the infusion rate exceeded an equivalent of 6-7 g/kg/d.[154-156] Accumulation of fat in pulmonary vessels found at necropsy in infants who died after receiving parenteral fat was also seen in those who died without receiving parenteral fat.[157,158] An increase in circulating free fatty acid levels can theoretically compete with bilirubin for binding to albumin. It was recommended that the free fatty acid to albumin ratio be kept below six[159] and that infants should receive no more than 1g/kg/d of parenteral fat if their serum bilirubin level is greater than 170 umol/l and their serum albumin is 30 g/l.[160] However, fat emulsion is also capable of binding unconjugated bilirubin[161] and infusions 2-4 g/kg/d have been found to have no effect on total or unbound serum bilirubin.[162,163] An association between parenteral fat administration and coagulase-negative staphylococcal bacteraemia in infants has been found[164] but there is no evidence that it impairs immune function in infants[165-168] A transient increase in blood glucose occurs with parenteral fat infusion and this was found to be due to alterations in glucose utilisation rather than enhanced glucose production.[169] Lipaemia does interfere with biochemical tests, leading to spurious conjugated hyperbilirubinaemia, hypercalcaemia and hyponatraemia. Curently available parenteral fat emulsions do not contain long-chain polyunsaturated fatty acids of the n-6 and n-3 family which are deposited in developing tissues such as the brain. Infants are incapable of synthesising these fatty acids and prolonged parenteral nutrition may result in a deficiency which is of potential importance.

Cholestatic jaundice occurs in 10-40% of infants on parenteral nutrition. It is very uncommon with short-term total parenteral nutrition of less than two weeks but it has been reported that 80% of those who required total parenteral nutrition for more than two months developed cholestasis.[170] Some of the possible mechanisms that have been suggested include immaturity of the hepatobiliary system,[171] prolonged fasting,[172] impaired bile secretion and bile salt formation,[173] coexisting sepsis,[174] underlying medical conditions associated with hypoxia or gastrointestinal conditions requiring surgery,[175] taurine deficiency,[176] excessive amino acid and glucose intake[177,178] and deficiency of antioxidants such as vitamin E.[179] The hypothesis that parenteral fat is associated with cholestasis, cannot be confirmed.[180] The administration of oral gentamicin[181] and parenteral metronidazole[182] in infants on prolonged parenteral nutrition have been found to be protective against cholestasis, suggesting possible involvement of intestinal flora in the pathogenesis of this condition. With few exceptions, cholestasis resolves when enteral feeding is commenced but it is known to progress to biliary cirrhosis[183] and liver failure.[184] Rapid recovery following phenobarbitone therapy[185] and biliary irrigation[186] has been reported.

In view of the potential hazards, parenteral nutrition is contraindicated in infants with fulminating sepsis prior to adequate stabilisation with antibiotic and supportive therapy. It should also be withheld in infants with severe circulatory instability or acute renal failure.

TRANSITION TO ENTERAL FEEDING

In spite of the adequacy of parenteral nutrition in meeting nutritional requirements for postnatal growth after birth, enteral feeding itself is vital for adaptation to extrauterine nutrition through its trophic effects on the gastrointestinal tract and its physiological effects on gastrointestinal exocrine and endocrine secretion and motility.[187] Milk feeds result in surges of secretin, glucagon, gastrin and motilin, all of which have trophic effects and mediate gastrointestinal secretion and motility. Parenterally fed young animals demonstrate not only a failure of growth of the stomach, small intestine and pancreas compared with those enterally-fed, but also a decrease in disaccharidase activity in the atrophic proximal small intestine mucosa.[188] It has been shown in human infants that enteral feeding is necessary for normal gastric acid secretion.[189] Enteral feeding is associated with increases in blood gastrin and motilin levels[190] and intestinal motor activity.[191] A higher whole body nitrogen turnover rate in enterally fed infants compared with those on parenteral nutrition is believed to reflect the rapid growth and development of the gut during enteral feeding.[192] Glucagon, in addition to its role in gastrointestinal motility, stimulates bile flow.[193] Infants on total parenteral nutrition with no enteral intake secrete extremely dilute bile, thus explaining the cholestasis associated with prolonged parenteral nutrition when it is associated with complete fasting.[194] Those who are parenterally fed also have significantly fewer immunoglobulin-containing intestinal plasma cells than those who are enterally fed.[195]

Instead of prolonged total parenteral nutrition, the early introduction of small quantities of milk is therefore beneficial for growth, development and maintenance of normal structure and function in the gastrointestinal and hepatobiliary systems.[196] Supplemental parenteral nutrition is becoming more widely accepted in neonatal practice with the realisation that gastrointestinal function has a continuous spectrum ranging from normal to virtually nil, and that between these extremes there is an intermediate group in whom an adequate nutritional intake can be achieved using the enteral route to meet some nutritive requirements and the parenteral route to supply the remainder. Early introduction of enteral feeding is associated with a lower prevalence of severe feeding intolerance[197] and nosocomial infection.[142] RCTs have compared the effects of early (2-7 days) versus late (9-18 days) enteral feeding, both groups initially receiving the majority of their energy intake by the parenteral route.[198,199] Infants who received early low-volume enteral feeding had improved feeding tolerance, reached full enteral nutrition faster and had less indirect hyperbilirubinaemia, cholestatic jaundice and osteopenia of prematurity.

Instead of prolonged total parenteral nutrition, the early introduction within one week after birth of a sub-nutritional quantity of milk is therefore recommended. As tolerance to enteral feeding improves over the ensuing days or weeks, the milk volume can be increased gradually. The risks of enteral feeding are therefore minimised with the slow grading up of feeds, during which time the parenteral route is relied upon to supply the necessary nutrients for optimal growth and development.

CONCLUSIONS

Parenteral nutrition represents a major breakthrough in the ability to provide adequate nutrition and to achieve normal growth in many preterm or sick infants who cannot tolerate or utilise enteral nutrients for long periods.[200] Because of the potential risks, it should only be used in neonatal units where there are appropriate facilities and staff who are obsessive with attention to detail. Many of its potential contributions toward improving the patient's short- and long-term outcome compared with conventional feeding have not been definitely proven, Nevertheless, it is life-saving in many instances of neonatal gastrointestinal failure. Therefore, its use in carefully selected infants who can be adequately cared for and monitored is to be recommended.

REFERENCES

1. CHURELLA HR, BACHHUBER WL, MACLEAN WC JR: Survey: methods of feeding low birth weight infants. Pediatrics 1985;76:243-9
2. HEIMLER R, DOUMAS BT, JENDRZEJCZAK BM, NEMETH PB, HOFFMAN RG, NELIN LD: Relationship between nutrition, weight change, and fluid compartments in preterm infants during the first week of life. J Pediatr 1993;122:110-4.
3. LORENZ JM, KLEINMAN LI, KOTAGAL UR, RELLER MD: Water balance in very low birth weight infants: relationship to water and sodium intake and effect on outcome. J Pediatr 1982; 01:423-32.
4. GILL A, YU VYH, BAJUK B, ASTBURY J: Postnatal growth in infants born before 30 weeks' gestation. Arch Dis Child 1986;61:549-53
5. RUTTER N, HULL D: Water loss from the skin of term and preterm babies. Arch Dis Child 1979; 54: 858-68
6. HAMMERLUND K, SEDIN G, STROMBERG B: Transepidermal water loss in newborn infants. Relation to gestational age and postnatal age in appropriate and small for gestational age infants. Acta Paediatr Scand 1983;72:721-8
7. WU PYK, HODGMAN JE: Insensible water loss in preterm infants: changes with postnatal development and non-ionizing radiant energy. Pediatrics 1974;54:704-18
8. BELL EF, GRAY JC, WEINSTEIN MR, OH W. The effects of thermal environment on heat balance and insensible water loss in low birth weight infants. J Pediatr 1980;96:452-9
9. OKKEN A, BLIJHAM C, FRANZ W, BOHN E: Effects of forced convection of heated air on insensible water loss and heat loss in preterm infants in incubators. J Pediatr 1982;101:108-12
10. MARKS KH, FARRELL TP, FRIEDMAN Z, MAISELS MJ: Intravenous alimentation and insensible water loss in low birth weight infants. Pediatrics 1979;63:543-6
11. FANAROFF AA, WALD M, GRUBER HS, KLAUS MH: Insensible water loss in low birth weight infants. Pediatrics 1972;50:236-45
12. BAUMGART S, ENGLE WD, FOX WW, POLIN RA: Effect of heat shielding on convective and evaporative heat loss and on radiant heat transfer in the premature infants. J Pediatr 1981;99:948-5
13. BAUMGART S: Reduction of oxygen consumption, insensible water loss and radiant heat demand with use of a plastic blanket for low birth weight infants under radiant warmers. Pediatrics 1984;74:1022-8
14. HARPIN VA, RUTTER N: Humidification of incubators. Arch Dis Child 1985;60:219-24
15. NASH MA: The management of fluid and electrolyte disorders in the neonate. Clin Perinatol 1981;8:251-62
16. SINCLAIR JC, DRISCOLL JM, HEIRD WC, WINTERS RW: Supportive management of the sick neonate. Pediatr Clin N Am 1970;17:863-93
17. REICHMAN BL, CHESSEX P, PUTET G, et al: Partition of energy metabolism and energy cost of growth in the very low birth weight infant. Pediatrics 1982;69:446-51
18. HEIMLER R, DOUMAS BT, JENDRZEJCZAK BM, NEMETH PB, HOFFMAN RG, NELIN LD: Relationship between nutrition, weight change, and fluid compartments in preterm infants during the first week of life. J Pediatr 1993;122:110-4
19. RUBECZ I, MESTYAN J: Energy metabolism and intravenous nutrition of premature infants. Biol Neonate 1973;23:45-58
20. ZLOTKIN SH, BRYAN MH, ANDERSON GH: Intravenous nitrogen and energy intakes required to duplicate in utero nitrogen accretion in prematurely born human infants. J Pediatr 1981;99:115-20
21. CHESSEX P, ZEBICHE H, PINEAULT M, LOPAGE D, DALLAIRE L: Effect of aminoacid composition of parenteral solutions on nitrogen retention and metabolic response in very low birth weight infants. J Pediatr 1985;106:111-7
22. WAHLIG TM, GEORGIEFF MK: The effects of illness on neonatal metabolism and nutritional management. Clin Perinatol 1995; 22: 77-96
23. KOH THHG, AYNSLEY-GREEN A, TARBIT M, EYRE JA: Neural dysfunction during hypoglycaemia. Arch Dis Child 1988; 63: 1353-8
24. LUCAS A, MORLEY R, COLE TJ: Adverse neurodevelopmental outcome of moderate neonatal hypoglycaemia. Br Med J 1988; 297: 1304-8
25. AULD PAM, BHANGANANDA P, MEHTA S: The influence of an early caloric intake with I-V glucose on catabolism of premature infants. Pediatrics 1966; 37: 592-6
26. STONESTREET BS, RUBIN L, POLLAK A, COWETT RM, OH W: Renal functions of low birth weight infants with hyperglycemia and glucosuria produced by glucose infusion. Pediatrics 1980;66:561-7
27. LOUIK C, MITCHELL AA, EPSTEIN MF, SHAPIRO S: Risk factors for neonatal hyperglycemia associated with 10% dextrose infusion. Am J Dis Child 1985; 139: 783-6
28. LILIEN LD, ROSENFIELD RL, BACCARO MM, PHILDES RS: Hyperglycemia in stressed small premature neonates. J Pediatr 1979;94:454-9
29. POLLAK A, COWETT RM, SCHWARTZ R, OH W: Glucose disposal in low birth weight infants during steady state hyperglycemia: effects of exogenous insulin administration. Pediatrics 1978;61:546-9
30. COWETT RM, ANDERSON GE, MAGUIRE CA, OH W: Ontogeny of glucose homeostasis in low birth weight infants. J Pediatr 1988; 112: 462-5
31. YU VYH, JAMES BE, HENDRY PG, MACMAHON RA: Glucose tolerance in very low birthweight infants. Aust Paediatr J 1979;15:147-51
32. OSTERTAG SG, JOVANOVIC L, LEWIS B, AULD PAM: Insulin pump therapy in the very low birth weight infant. Pediatrics 1986; 78: 625-30
33. BINDER ND, RASCHKO RK, BENDA GI, REYNOLDS JW: Insulin infusion with parenteral nutrition in extremely low birthweight infants with hyperglycemia. J Pediatr 1989;114:273-80
34. COLLINS JW JR, HOPPE M, BROWN K, EDIDIN DV, PADBURY J, OGATA ES: A controlled trial of insulin infusion and parenteral nutrition in extremely low birth weight infants with glucose intolerance. J Pediatr 1991; 118: 921-7
35. SAINI J, MACMAHON P, MORGAN JB, KOVAR IZ: Early parenteral feeding of amino acids. Arch Dis Child 1989; 64: 1362-6
36. RIVERA A JR, BELL EF, BIER DM: Effect of intravenous amino acids on protein metabolism of preterm infants during the first three days of life. Pediatr Res 1993; 33: 106-11
37. RIVERA A JR, BELL EF, STEGINK LD, ZIEGLER EE: Plasma amino acid profiles during the first three days of life in infants with respiratory distress syndrome: effect of parenteral amino acid supplementation. J Pediatr 1989;115:465-8.
38. SHAW JCL: Parenteral nutrition in the management of sick low birthweight infants. Pediatr Clin N Am 1973;20:333-57
39. HEIRD WC, HAY W, HELMS RA, STORM MC, KASHYAP S, DELL RB: Pediatric parenteral amino acid mixture in low birth weight infants. Pediatrics 1988;81:41-50
40. DUFFY B, PENCHARZ P: The effects of surgery on the nitrogen metabolism of parenterally fed human neonates. Pediatr Res 1986; 20: 32-5
41. VAN GOUDOEVER JB, WATTIMENA JDL, CARNIELLI VP, SULKERS EJ, DEGENHART HJ, SAUER PJJ: Effect of dexamethasone on protein metabolism in infants with bronchopulmonary dysplasia. J Pediatr 1994; 124: 112-8
42. SCHANLER RJ, SHULMAN RJ, PRESTRIDGE LL: Parenteral

nutrient needs of very low birth weight infants. J Pediatr 1994;125:961-8
43. LAIDLAW SA, KOPPLE JD: Newer concepts of the indispensable amino acids. Am J Clin Nutr 1987; 46: 593-605
44. ANDERSON GE, BUCHER D, FRIIS-HANSEN B, NEXO E, OLESEN H: Plasma amino acid concentrations in newborn infants during parenteral nutrition. J Parenter Enteral Nutr 1983; 7: 369-73
45. CORAN AG, DRONGOWSKI RA: Studies on the toxicity and efficacy of a new amino acid solution in pediatric parenteral nutrition. J Parenter Enteral Nutr 1987;11:368-77
46. PUNTIS JW, BALL PA, PREECE MA, GREEN A, BROWN GA, BOOTH IW: Egg and breast milk based nitrogen sources compared. Arch Dis Child 1989; 64: 1472-7
47. MITTON SG, BURSTON D, BRUETON MJ, KOVAR IZ: Plasma amino acid profiles in preterm infants receiving Vamin 9 glucose or Vamin Infant. Early Hum Dev 1993; 32: 71-8
48. LUCAS A, BAKER BA, MORLEY RM: Hyperphenylalaninaemia and outcome in intravenously fed preterm infants. Arch Dis Child 1993; 68: 579-83
49. ROSENTHAL M, SINHA S, LAYWOOD E, LEVENE M: A double blind comparison of a new paediatric amino acid solution in neonatal total parenteral nutrition. Early Hum Develop 1987;15:137-46
50. HELMS RA, CHRISTENSEN ML, MAUER EC, STORM MC: Comparison of a pediatric versus standard amino acid formulation in preterm neonates requiring parenteral nutrition. J Pediatr 1987; 110: 466-70
51. MALLOY MH, RASSIN DK, RICHARDSON CJ: Total parenteral nutrition in sick preterm infants: effects of cysteine supplementation with nitrogen intakes of 240 and 400 mg/kg/day. J Pediatr Gastroenterol Nutr 1984; 3: 239-44
52. THORNTON L, GRIFFIN E: Evaluation of a taurine containing amino acid solution in parenteral nutrition. Arch Dis Child 1991; 66: 21-5
53. IMURA K, OKADA A, FUKUI Y, et al: Clinical Studies on a newly devised amino acid solution for neonates. J Parenter Enteral Nutr 1988; 12: 496-504
54. CLARK D, HENDERSON M, SMITH M, DEAR PRF: Plasma amino acid concentrations in parenterally fed preterm infants. Arch Dis Child 1989; 64: 939-42
55. HANNING RM, ZLOTKIN SH: Amino acid and protein needs of the neonate: effect of excess and deficiency. Sem Perinatol 1989; 13: 131-41
56. PINEAULT M, CHESSEX P, BISAILLON S, BRISSON G: Total parenteral nutrition in the newborn: impact of the quality of infused energy on nitrogen metabolism. Am J Clin Nutr 1988; 47: 298-304
57. VAN AERDE JE, SAUER PJ, PENCHARZ PB, SMITH JM, HEIM T, SWYER PR: Metabolic consequences of increasing energy intake by adding lipid to parenteral nutrition in full-term infants. Am J Clin Nutr 1994; 59: 659-62
58. LEE EJ, SIMMER K, GIBSON RA: Essential fatty acid deficiency in parenterally fed preterm infants. J Paediatr Child Health 1993; 29: 51-5
59. COOKE RJ, ZEE P, YEH Y: Safflower oil emulsion administration during parenteral nutrition in the preterm infant. Effect on essential fatty acid status. J Pediatr Gastroenterol Nutr 1985; 4: 799-803
60. MCCLEAD RE JR, MENG HC, GREGORY SA, BUDDE C, SLOAN HR: Comparison of the clinical and biochemical effect of increased linolenic acid in a safflower oil intravenous fat emulsion. J Pediatr Gastroenterol Nutr 1985; 4: 234-9
61. RUBIN M, HARELL D, NAOR N, et al: Lipid infusion with different triglyceride cores (long-chain vs medium-chain/long-chain triglycerides): effect on plasma lipids and bilirubin binding in premature infants. J Parenter Enteral Nutr 1991; 15: 642-6
62. LIMA LAM, MURPHY JF, STANSBIE D, ROWLANDON P, GRAY OP: Neonatal parenteral nutrition with a fat emulsion containing medium chain triglycerides. Acta Paediatr Scand 1988; 77: 332-39
63. UHLEMANN M, PLATH C, HEINE W, et al: MCT fat emulsions enhance efficacy of whole-body protein metabolism in very small preterm neonates. Clin Nutr 1989; 8: 84
64. SHENNAN AT, BRYAN MH, ANGEL A: The effects of gestational age on Intralipid tolerance in newborn infants. J Pediatr 1977; 91: 134-7
65. BRANS YW, ANDREW DS, CARILLO DW, DUTTON EB, MENCHACA EM, PULEO-SCHEPPKE BA: Tolerance of fat emulsions in very low birthweight neonates: effect of birthweight on plasma lipid concentrations. Am J Perinatol 1990; 7: 114-7
66. ROVAMO LM, NIKKILA EA, RAIVIO KO: Lipoprotein lipase, hepatic lipase, and carnitine in premature infants. Arch Dis Child 1988; 63: 140-7
67. SCHIFF D, CHAN G, SECOMBE D, HAHN P: Plasma carnitine levels during intravenous feeding of the neonate. J Pediatr 1979; 95: 1043-6
68. PENN D, SCHMIDT-SOMMERFELD E, WOLF H: Carnitine deficiency in premature infants receiving total parenteral nutrition. Early Hum Dev 1980; 4: 23-34
69. YEH YH, COOKE RJ, ZEE P: Impairment of lipid emulsion metabolism associated with carnitine insufficiency in premature infants. J Pediatr Gastroenterol Nutr 1985; 4: 795-8
70. SCHMIDT-SOMMERFELD E, PENN D, WOLF H: Carnitine deficiency in premature infants receiving total parenteral nutrition: Effect of L-carnitine supplementation. J Pediatr 1983; 102: 931-5
71. ORZALI A, DONZELLI F, ENZI G, RUBALTELLI FF: Effect of carnitine on lipid metabolism in the newborn. I. Carnitine supplementation during total parenteral nutrition in the first 48 hours of life. Biol Neonate 1983; 43: 186-90
72. CORAN AG, DRONGOWSKI RA, BAKER PJ: The metabolic effects of oral L-carnitine administration in infants receiving total parenteral nutrition with fat. J Pediatr Surg 1985; 20: 758-64
73. BONNER CM, DEBRIE KL, HUG G, LANDRIGAN E, TAYLOR BJ: Effects of parenteral L-carnitine supplementation on fat metabolism and nutrition in premature infants. J Pediatr 1995; 126: 287-92
74. HELMS RA, WHITINGTON PF, MAUER EC, CATARAU EM, CHRISTENSEN ML, BORUM PR: Enhanced lipid utilization in infants receiving oral L-carnitine during long-term parenteral nutrition. J Pediatr 1986; 109: 984-8
75. CHRISTENSEN ML, HELMS RA, MAUER EC, STORM MC: Plasma carnitine concentration and lipid metabolism in infants receiving parenteral nutrition. J Pediatr 1989; 115: 794-8
76. GILBERTSON N, KOVAR IZ, COX DJ, CROWE L, PALMER NT: Introduction of intravenous lipid administration on t he first day of life in the low birth weight neonate. J Pediatr 1991; 119: 615-23
77. SOSENKO IRS, RODRIGUEZ-PIERCE M, BANCALARI E: Effect of early initiation of intravenous lipid administration on the incidence and severity of chronic lung disease in premature infants. J Pediatr 1993; 123: 975-82
78. BROWNLEE KG, KELLY EJ, NG PC, KENDALL-SMITH SC, DEAR PR: Early or late parenteral nutrition for the sick preterm infant? Arch Dis Child 1993; 69: 281-3
79. PITKANEN O, HALLMAN M, ANDERSON S: Generation of free radicals in lipid emulsion used in parenteral nutrition. Pediatr Res 1991; 29: 56-9
80. NEUZIL J, DARLOW BA, INDER TE, SLUIS KB, WINTERBOURN CC, STOCKER R: Oxidation of parenteral lipid emulsion by ambient and phototherapy lights: potential toxicity of routine parenteral feeding. J Pediatr 1995; 126: 785-90
81. HILLIARD JL, SHANNON DL, HUNTER MA, BRANS YW: Plasma lipid levels in preterm neonates receiving parenteral nutrition. Arch Dis Child 1983; 58: 29-33
82. CHESSEX P, GAGNE G, PINEAULT M, VAUCHER J, BISAILLON S, BRISSON G: Metabolic and clinical consequences of changing from high-glucose to high-fat regimens in parenterally fed newborn infants. J Pediatr 1989; 115: 992-7
83. PARK W, PAUST H, BROSICKE H, KNOBLACK G, HELGE H: Impaired fat utilization in parenterally fed low birth weight infants suffering from sepsis. J Parenter Enteral Nutr 1986; 10: 627-30
84. HAUMONT D, DECKELBAUM RJ, RICHELLE M, et al: Plasma lipid and plasma lipoprotein concentrations in low birth weight infants given parenteral nutrition with twenty or ten percent lipid emulsion. J Pediatr 1989; 115: 787-93
85. HAUMONT D, RICHELLE M, DECKELBAUM RJ, COUSSAERT E, CARPENTIER YA: Effect of liposomal content of lipid emulsions on plasma lipid concentrations in low birth weight infants receiving parenteral nutrition. J Pediatr 1992; 121: 759-63
86. KAO LC, CHENG MH, WARBURTON D: Triglycerides, free fatty acids, free fatty acids/albumin molar ratio, and cholesterol levels in serum of neonates receiving long-term lipid infusions: controlled trial of continuous and intermittent regimes. J Pediatr 1984; 104: 429-35
87. BRANS YW, ANDREW DS, CARRILLO DW, DUTTON EP, MENCHACA EM, PULEO-SCHAPPKE BA: Tolerance of fat emulsions in very low birth weight neonates. Am J Dis Child 1988; 142: 145-52
88. SCHREINER RL, GLICK MR, NORDSCHOW CD, GRESHAM EL: An evaluation of methods to monitor infants receiving intravenous lipids. J Pediatr 1979; 94: 197-200
89. PAUST H, SCHRODER H, PARK W, JAKOBS C, FRAUENDIENST G: Fat elimination in parenterally fed low birthweight infants during the first two weeks of life. J Parenter Enteral Nutr 1983; 7: 557-9
90. COOKE RJ, YEH Y, GIBSON D, DEBO D, BELL GL: Soybean oil emulsion administration during parenteral nutrition in the preterm infant: effect on essential fatty acid, lipid and glucose metabolism. J Pediatr 1987; 111: 767-73
91. REES L, SHAW JCL, BROOK CGD, FORSLING ML: Hyponatraemia in the first week of life in preterm infants. II Sodium and water balance. Arch Dis Child 1984; 59: 423-9

92. AL-DAHHAN J, HAYCOCK GB, CHANTLER C, STIMMLER L: Sodium homeostasis in mature and immature neonates. I Renal aspects. Arch Dis Child 1983;58:335-42.
93. GRUSKAY J, COSTARINO AT, POLIN RA, BAUMGART S: Nonoliguric hyperkalemia in the premature infant weighing less than 1000 grams. J Pediatr 1988; 113: 381-6
94. BRION LP, SCHWARTZ GJ, CAMPBELL D, FLEISCHMAN AR: Early hyperkalaemia in very low birthweight infants in the absence of oliguria. Arch Dis Child 1989; 64: 270-82
95. GROH-WARGO S, CIACCIA A, MOORE J: Neonatal metabolic acidosis: effect of chloride from normal saline flushes. J Parenter Enteral Nutr 1988; 12: 159-61
96. SALLE BL, DAVID L, CHOPARD JP, GRAFMEYER DC, RENAUD H: Prevention of early neonatal hypocalcemia in low birth weight infants with continuous calcium infusion: effect on serum calcium, phosphorus, magnesium, and circulating immunoactive parathyroid hormone and calcitonin. Pediatr Res 1977; 11: 1180-5
97. KOO WW, TSANG RC, SUCCOP P, KRUG-WISPE SK, BABCOCK D, OESTREICH AE: Minimal vitamin D and high calcium and phosphorus needs of preterm infants receiving parenteral nutrition. J Pediatr Gastroenterol Nutr 1989; 8: 225-33
98. VILEISIS RA: Effect of phosphorus intake in total parenteral nutrition infusates in premature infants, J Pediatr 1987; 110: 586-90
99. PRESTRIDGE LL, SCHANLER RJ, SHULMAN RJ, BURNS PA, LAINE LL: Effect of parenteral calcium and phosphorus therapy on mineral retention and bone mineral content in very low birth weight infants. J Pediatr 1993; 122: 761-8
100. GREENE HL, HAMBRIDGE KM, SCHANLER R, TSANG RC: Guidelines for the use of vitamins, trace elements, calcium, magnesium and phosphorus in infants and children receiving total parenteral nutrition: report of the Subcommittee on Pediatric Parenteral Nutrition Requirements from the Committee on Clinical Practice Issues of the American Society for Clinical Nutrition. Am J Clin Nutr 1988; 48: 1324-42
101. MORENO A, DOMINGUEZ C, BALLABRIGA A: Aluminium in the neonate related to parenteral nutrition. Acta Paediatr 1994:83:25-9
102. GILLES J, JONES G, PENCHARZ P: Delivery of vitamins A, D and E in parenteral nutrition solutions. J Parenter Enteral Nutr 1983; 7: 11-4
103. SMITH JL, CANHAM JE, WELLS PA: Effect of phototherapy light, sodium bisulfite, and pH on vitamin stability in total parenteral nutrition and mixtures. J Parenter Enteral Nutr 1988; 12: 394-402
104. BAECKERT PA, GREENE HL, FRITZ I, OELBERG DG, ADCOCK EW: Vitamin concentrations in very low birth weight infants given vitamins intravenously in a lipid emulsion: measurement of vitamins A, D and E and riboflavin. J Pediatr 1988; 113: 1057-63
105. DAHL GB, SVENSSON L, KINNANDER NJG, ZANDER M, BERSTROM UK: Stability of vitamins in soybean oil fat emulsion under conditions simulating intravenous feeding of neonates and children. J Parenter Enteral Nutr 1994; 18: 234-9
106. MAY F, ROBBINS G: A computer program for parenteral nutrition solution preparation. J Parenter Enteral Nutr 1978; 2: 646-51
107. GIACOIA GP, CHOPRA R: The use of a computer in parenteral alimentation of low birth weight infants. J Parenter Enteral Nutr 1981; 5: 329-31
108. GALE R, GALE J, BRANSKI D, ARMON Y, ZELINGHER J, ROLL D: An interactive microcomputer program for calculation of combined parenteral and enteral nutrition for neonates. J Pediatr Gastroenterol Nutr 1983; 2: 653-8
109. WILSON FE, YU VYH, HAWGOOD S, ADAMSON TM, WILKINSON MH: Computerised nutritional data management in neonatal intensive care. Arch Dis Child 1983; 58: 732-6
110. MACMAHON P: Prescribing and formulating neonatal intravenous feeding solutions by microcomputer. Arch Dis Child 1984; 59: 548-52
111. HARPER RG, CARRERA E, WEISS S, LUONGO M: A complete computerized program for nutritional management in the neonatal intensive care nursery. Am J Perinatol 1985; 2: 161-2
112. YAMAMOTO LG, GAINSLEY GJ, WITEK JE: Pediatric parenteral nutrition management using a comprehensive user-friendly computer program designed for personal computers. J Parenter Enteral Nutr 1986; 10: 535-9
113. DICE JE, BURCKART GJ, WOO JT, HELMS RA: Standardized versus pharmacist-monitored individualized parenteral nutrition in low birth weight infants. Am J Hosp Pharm 1981; 8: 1487-9
114. RAUPP P, VON KRIES R, SCHMIDT E, PFAHL H, GUNTHER O: Incompatibility between fat emulsion and calcium plus heparin in parenteral nutrition of premature babies. Lancet 1988; i: 700
115. BATTON DG, MAISELS J, APPELBAUM P: Use of peripheral intravenous cannulas in premature infants: a controlled study. Pediatrics 1982; 70: 487-90
116. PHELPS SJ, HELMS RA: Risk factors affecting infiltration of peripheral venous lines in infants. J Pediatr 1987; 111: 384-9
117. CHATHAS MK, PATON JB, FISHER DE: Percutaneous central venous catheterization. Am J Dis Child 1990; 144: 1246-50
118. NAKAMURA KT, SATO Y, ERENBERG A: Evaluation of a percutaneously placed 27-gauge central venous catheter in neonates weighing <1200 grams. J Parenter Enteral Nutr 1990; 14: 295-9
119. NEUBAUER AP: Percutaneous central i.v. access in the neonate: experience with 535 silastic catheters. Acta Paediatr 1995; 84: 756-60
120. SHULMAN RJ, POKORNY WJ, MARTIN CG, PETITT R, BALDAIA L, RONEY D: Comparison of percutaneous and surgical placement of central venous catheters in neonates. J Pediatr Surg 1986; 21: 348-50
121. OGATA ES, SCHULMAN S, RAFFENSPERGER J, LUCK S, RUSNAK M: Caval catheterisation in the intensive care nursery: a useful means for providing parenteral nutrition to the extremely low birthweight infant. J Pediatr Surg 1984; 19: 258-62
122. WARNER BW, GORGONE P, SCHILLING S, FARELL M, GHORY MJ: Multiple purpose central venous access in infants less than 1000 grams. J Pediatr Surg 1987; 22: 820-2
123. ALPAN G, EYAL F, SPRINGER C, GLICK B, GODER K, ARMON J: Heparinization of alimentation solutions administered through peripheral veins in premature infants: a controlled study. Pediatrics 1984; 74: 374-8
124. NEUBAUER AP: Percutaneous central i.v. access in the neonate: experience with 535 silastic catheters. Acta Paediatr 1995; 84:756-60.
125. BRISMAR B, HARDSTEDT C, JACOBSON S, KAGER L, MALMBORG A: Reduction of catheter-associated thrombosis in parenteral nutrition by intravenous heparin therapy. Arch Surg 1982; 117: 1196-9
126. PHELPS SJ, COCHRAN EB: Peripheral venous line infiltration in infants receiving 10% dextrose, 10% dextrose/amino acids, or 10% dextrose/amino acids/fat emulsion. J Parenter Enteral Nutr 1989;13: 628-32
127. YU VYH, JAMES B, HENDRY P, MACMAHON RA: Total parenteral nutrition in very low birthweight infants: a controlled trial. Arch Dis Child 1979; 54: 653-61
128. KANAREK KS, KUZNICKI MB, BLAIR RC: Infusion of total parenteral nutrition via the umbilical artery. J Parenter Enteral Nutr 1991; 15: 71-4
129. PEREIRA GR, LIM BK, ING C, MEDEIROS HF: Umbilical vs peripheral vein catheterization for parenteral nutrition in sick premature neonates. Yonsei Med J 1992; 33: 224-31
130. GUNN T, REAMAN G, OUTERBRIDGE EW, COLE E: Peripheral total parenteral nutrition for premature infants with the respiratory distress syndrome: A controlled study. J Pediatr 1978; 92: 608-13
131. BRYAN MH, WEI P, HAMILTON JR, CHANCE GW, SWYER PR: Supplemental intravenous alimentation in low birth weight infants. J Pediatr 1973; 82: 940-4
132. PILDES RS, RAMAMURTHY RS, CORDERO GV, WONG PWK: Intravenous supplementation of L-amino acids and dextrose in low-birth-weight infants. J Pediatr 1973; 82: 945-50
133. BRANS YW, SUMNERS JE, DWECK HS, CASSADY G: Feeding the low birth weight infant: orally or parenterally? Preliminary results of a comparative study. Pediatrics 1974; 54: 15-22
134. ABITBOL CL, FELDMAN DB, AHMANN P, RUDMAN D: Plasma amino acid patterns during supplemental intravenous nutrition of low birthweight infants. J Pediatr 1975; 86: 766-72
135. ANDERSON TL, MUTTART CR, BIEBER MA, NICHOLSON JF, HEIRD WC: A controlled trial of glucose versus glucose and amino acids in premature infants. J Pediatr 1979; 94: 947-51
136. POLLEY TZ, BENNER JW, RHODIN A, WEINTRAUB WH, CORAN AG: Changes in total body water in infants receiving total intravenous nutrition. J Surg Res 1979; 26: 555-9
137. CORAN AG, DRONGOWSKI RA, WESLEY JR: Changes in total body water and extracellular fluid volume in infants receiving total parenteral nutrition. J Pediatr Surg 1984; 19: 771-6
138. GEORGIEFF MK, MILLS MM, LINDEKE L, IVERSON S, JOHNSON DE, THOMPSON TR: Changes in nutritional management and outcome of very low birth weight infants. Am J Dis Child 1989; 143: 82-5
139. YU VYH: Cardiorespiratory response to feeding in newborn infants. Arch Dis Child 1976; 51: 305-9
140. EYAL F, SAGI E, ARAD I, AVITAL A: Necrotising enterocolitis in the very low birthweight infant: expressed breast milk feeding compared with parenteral feeding. Arch Dis Child 1982; 57: 274-6
141. GLASS EJ, HUME R, LANG MA, FORFAR JO: Parenteral nutrition compared with transpyloric feeding. Arch Dis Child 1984; 59: 131-5
142. UNGER A, GOETZMAN BW, CHAN C, LYONS AB, MILLER

MF: Nutritional practices and outcome of extremely premature infants. Am J Dis Child 1986; 140: 1027-33
143. MCKEOWN RE, MARSH TD, AMARNATH U, GARRISON CZ, ADDY CL, THOMPSON SJ, AUSTIN JL: Role of delayed feeding and of feeding increments in necrotizing enterocolitis. J Pediatr 1992; 121: 764-70
144. MOYER-MILEUR L, CHAN GM: Nutritional support of very low birth weight infants requiring prolonged assisted ventilation. Am Journal of Dis Child 1986; 140: 929-32
145. HEIRD WC: Parenteral feeding. In: Sinclair JC, Bracken MB. (eds) Effective Care of the Newborn Infant. Oxford University Press. Oxford 1992; 141-60
146. BEGANOVIC N, VERLOOVE-VANHORICK SP, BRAND R, RUYS JH: Total parenteral nutrition and sepsis. Arch Dis Child 1988; 63: 66-9
147. WEESE-MAYER DE, FONDRIEST DW, BROUILETTE RT, SHULMAN ST: Risk factors associated with candidemia in the neonatal intensive care unit: a case control study. Pediatr Infect Dis J 1987; 6: 190-6
148. AZIMI PH, LEVERNIER K, LEFRAK LM, et al: Malassezia furfur: a cause of occlusion of percutaneous central venous catheters in infants in the intensive care nursery. Pediatr Infect Dis J 1988; 7: 100-3
149. PUNTIS JW, HOLDEN CE, SMALLMAN S, FINKEL Y, GEORGE RH, BOOTH IW: Staff training: a key factor in reducing intravascular catheter sepsis. Arch Dis Child 1991; 66: 335-7
150. FLEER A, SENDERS RC, VISSER MR, et al: Septicemia due to coagulase-negative staphylococci in a neonatal intensive care unit: clinical and bacteriological features and contaminated parenteral fluids as a source of sepsis. Pediatr Infect Dis 1983; 2: 426-31
151. JARVIS WR, HIGHSMITH AK, ALLEN JR, HALEY RW: Polymicrobial bacteremia associated with lipid emulsion in a neonatal intensive care unit. Pediatr Infect Dis 1983; 2: 203-8
152. HEIRD WC, NICHOLSON JR, DRISCOLL JM JR, SCHULLINGER JN, WINTERS RW: Hyperammonemia resulting from intravenous alimentation using a mixture of synthetic L-amino acids: a preliminary report. J Pediatr 1972; 82: 162-5
153. THOMAS DW, SINATRA FR, HACK SL, SMITH TM, PLATZKER ACG, MERRITT RJ: Hyperammonemia in neonates receiving intravenous nutrition. J Parenter Enteral Nutr 1982; 6: 503-6
154. ADAMKIN DH, GELKE KN, WILKERSON SA: Clinical and laboratory observations: influence of intravenous fat therapy on tracheal effluent phospholipids and oxygenation in severe respiratory distress syndrome. J Pediatr 1985; 106: 122-4
155. BRANS YW, DUTTON EB, ANDREW DS, MENCHACA EM, WEST DL: Fat emulsion tolerance in very low birth weight neonates: effect on diffusion of oxygen in the lungs and on blood pH. Pediatrics 1986; 78: 79-84
156. LLOYD TR, BOUCEK MM: Effect of Intralipid on the neonatal pulmonary bed: an echocardiac study. J Pediatr 1986; 108: 130-3
157. HERTEL J, TYGSTRUP I, ANDERSON GE: Intravascular fat accumulation after Intralipid infusion in the very low birthweight infant. J Pediatr 1982; 100: 975-6
158. SHULMAN RJ, LANGSTON C, SCHANLER RJ: Pulmonary vascular deposition after administration of intravenous fat to infants. Pediatrics 1987; 79: 99-102
159. ANDREW G, CHAN G, SCHIFF D: Lipid metabolism in the neonate. II. The effects of Intralipid on bilirubin binding in vitro and in vivo. J Pediatr 1976; 88: 279-84
160. HEIRD WC: Use of intravenous fat emulsions in pediatric patients. Pediatrics 1981; 68: 738-43
161. THALER MM, WENNBERG RP: Influence of intravenous nutrients on bilirubin transport. II. Emulsified lipid solutions. Pediatr Res 1977; 11: 167-71
162. SPEAR ML, STAHL GE, HAMOSH M, MCNELIS WG, RICHARDSON LL, SPENCE V: Effect of heparin dose and infusion rate on lipid clearance and bilirubin binding in premature infants receiving intravenous fat emulsions. J Pediatr 1988; 112: 94-8
163. BRANS YW, RITTER DA, KENNY JD, ANDREW DS, DUTTON EB, CARILLO DW: Influence of intravenous fat emulsion on serum bilirubin in very low birthweight infants. Arch Dis Child 1987; 62: 156-60
164. FREEMAN J, GOLDMAN DA, SMITH NE, SIDEBOTTOM DG, EPSTEIN MF, PLATT R: Association of intravenous lipid emulsion and coagulase-negative staphylococcal bacteremia in neonatal intensive care units. N Engl J Med 1990; 323: 301-8
165. ENGLISH D, ROLOFF JS, LUKENS JN, PARKER P, GREENE HL, GHISHAN FK: Intravenous lipid emulsions and human neutrophil function. J Pediatr 1981; 99: 913-6
166. HELMS RA, HERROD HG, BURCKART GJ, CHRISTENSEN ML: E-rosette formation, total T-cells, and lymphocyte transformation in infants receiving intravenous safflower oil emulsion. J Parenter Enteral Nutr 1983; 7: 541-5
167. STRUNK RC, MURROW BW, THILO E, KUNKE KS, JOHNSON EG: Normal macrophage function in infants receiving Intralipid by low-dose intermittent administration. J Pediatr 1985; 106: 640-5
168. USMANI SS, HARPER RG, USMANI SF: Effect of a lipid emulsion (Intralipid) on polymorphonuclear leukocyte functions in the neonate. J Pediatr 1988; 113: 132-6
169. YUNIS KA, OH W, KALHAN S, COWETT RM: Glucose kinetics following administration of an intravenous fat emulsion to low birth weight neonates. Am J Physiol 1992; 263: E844-9
170. BEALE EF, NELSON RM, BUCCIARELLI RL, DONNELLY WH, EITZMAN DV: Intrahepatic cholestasis associated with parenteral nutrition in premature infants. Pediatrics 1979; 64: 342-7
171. MERRITT RJ: Cholestasis associated with total parenteral nutrition. J Pediatr Gastroenterol Nutr 1986; 5: 9-22
172. RAGER R, FINEGOLD MJ: Cholestasis in immature newborn infants: is parenteral alimentation responsible? J Pediatr 1975;86:264-9.
173. SONDHEIMER JM, BRYAN H, ANDREWS W, FORSTER GG: Cholestatic tendencies in premature infants on and off parenteral nutrition. Pediatrics 1978; 62: 984-9
174. KUBOTA A, OKADA A, NEZU R, KAMATA S, IMURA K, TAKAGI Y: Hyperbilirubinemia in neonates associated with total parenteral nutrition. J Parenter Enteral Nutr 1988; 12: 602-6
175. BELL RL, FERRY GD, SMITH EO, et al: Total parenteral nutrition related cholestasis in infants. J Parenter Enteral Nutr 1986; 10: 356-9
176. COOPER A, BETTS JM, PEREIRA GR, ZEIGLER MM: Taurine deficiency in the severe hepatic dysfunction complicating total parenteral nutrition. J Pediatr Surg 1984; 19: 462-6
177. VILEISIS RA, INWOOD RJ, HUNT CE: Prospective controlled study of parenteral nutrition associated cholestatic jaundice: effects of protein intake. J Pediatr 1980; 96: 893-7
178. SANKARAN K, BERSCHEID B, VERMA V, ZAKHARY G, TAN L: An evaluation of total parenteral nutrition using Vamin and Aminosyn as protein base in critically ill preterm infants. J Parenter Enteral Nutr 1985; 9: 439-42
179. BERGER HM, DEN OUDEN AL, CALAME JJ: Pathogenesis of liver damage during parenteral nutrition: is lipofuscin a clue? Arch Dis Child 1985; 60: 774-6
180. BLACK DD, SUTTLE EA, WHITINGTON PF, WHITINGTON GL, KORONES SD: The effect of short-term total parenteral nutrition on hepatic function in the human neonate: a prospective randomised clinical study demonstrating alteration of hepatic canalicular function. J Pediatr 1981; 99: 445-9
181. SPURR SG, GRYLACK LJ, MEHTA NR: Hyperalimentation associated neonatal cholestasis: effect of oral gentamicin. J Parenter Enteral Nutr 1989; 13: 633-6
182. KUBOTA A, OKADA A, IMURA K, KAWAHARA H, NEZU R, KAMATA S, TAKAGI Y: The effect of metronidazole on TPN-associated liver dysfunction in neonates. J Pediatr Surg 1990; 25: 618-21
183. PEREIRA GR, SHERMAN MS, DIGIACOMO J, ZIELER M, ROTH K, JACOBOWSKI D: Hyperalimentation induced cholestasis. Am J Dis Child 1981; 135: 842-5
184. POSTUMA R, TREVENEN CL: Liver disease in infants receiving total parenteral nutrition. Pediatrics 1979; 63: 110-5
185. SOUTH M, KING A: Parenteral nutrition associated cholestasis: recovery following phenobarbitone. J Parenter Enteral Nutr 1987; 11: 208-9
186. COOPER A, ROSS AJ III, O'NEIL JA, BISHOP HC, TEMPLETON JM, ZIEGLER MM: Resolution of intractable cholestasis associated with total parenteral nutrition following biliary irrigation. J Pediatr Surg 1985; 20: 772-4
187. LUCAS A, BLOOM SR, AYNSLEY-GREEN A: Metabolic and endocrine effects of depriving preterm infants of enteral nutrition. Acta Paediatr Scand 1983; 72: 245-9
188. GOLDSTEIN RM, HEBIGUCHI T, LUK GD, TAQI F, FRANKLIN FA JR, NIEMIEC PW, DUDGEON D: The effects of total parenteral nutrition on gastrointestinal growth and development. J Pediatr Surg 1985;20:785-91
189. HYMAN PE, FELDMAN EJ, AMENT ME, BRYNE WJ, EULER AR: Effect of enteral feeding on the maintenance of gastric acid secretory function. Gastroenterology 1983; 84: 341-5
190. SHULMAN DI, KANAREK K: Gastrin, motilin, insulin, and insulin-like growth factor-I concentrations in very low birth weight infants receiving enteral or parenteral nutrition. J Parenter Enteral Nutr 1993; 17: 130-3

191. BERSETH CL, NORDYKE C: Enteral nutrients promote postnatal maturation of intestinal motor activity in preterm infants. Am J Physiol 1993; 264: G1046-51
192. DUFFY B, PENCHARZ P: The effect of feeding route (IV or oral) on the protein metabolism of the neonate. Am J Clin Nutr 1986; 43: 108-11
193. AYNSLEY-GREEN A: Plasma hormone concentrations during enteral and parenteral nutrition in the human newborn. J Pediatr Gastroenterol Nutr 1983; 2: 108-12
194. AL-RABEEAH A, THURSTON OG, WALKER K: Effect of total parenteral nutrition on biliary lipids in neonates. Can J Surg 1986; 29: 289-91
195. KNOX WF: Restricted feeding and human intestinal plasma cell development. Arch Dis Child 1986; 61: 744-9
196. BERSETH CL: Minimal enteral feedings. Clin Perinatol 1995; 22: 195-204
197. LAGAMMA EF, OSTERTAG SG, BIRENBAUM H: Failure of delayed oral feedings to prevent necrotizing enterocolitis. Am J Dis Child 1985; 139: 385-9.
198. 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: 622-9
199. SLAGLE TA, GROSS SJ: Effect of early low-volume enteral substrate on subsequent feeding tolerance in very low birth weight infants. J Pediatr 1988; 13: 526-31
200. YU VYH, MACMAHON RA: (eds) Intravenous Feeding of the Neonate. Edward Arnold, London 1992