Nutritional Problems and Catch-Up Growth in Infants with Intrauterine Growth Retardation

Philippe Chessex

Centre de recherche et service de néonatologie, Hôpital Sainte-Justine, Montreal, H3T 1C5 PQ, Canada

In the past, it was common practice to relate low birthweight to prematurity. However, a number of environmental, maternal, placental, and fetal factors have been recognized as causing intrauterine growth retardation (IUGR) in babies who are small-for-gestational-age (SGA). In the more affluent societies, one-third of the low birthweight babies are SGA. Yet in communities where protein-energy malnutrition and common infections are predominant environmental factors, the incidence of growth retardation due to intrauterine malnutrition can increase to 80% in low birthweight infants (1). The infant who has suffered from intrauterine malnutrition early in the third trimester of pregnancy is potentially at risk of continued growth retardation (2-4) as well as of learning and behavioral problems (5-7). Therefore, perinatal problems must be focused on the prevention of intrauterine growth retardation (1).

In the presence of a newborn baby with intrauterine growth retardation, one of the challenging therapeutic problems is to decide when, what, and how to feed this low birthweight infant. In this chapter we shall be concerned with some physiological adaptations and metabolic consequences which modulate such decisions.

INTRAUTERINE MALNUTRITION

Several different etiological factors are associated with IUGR (8-11), explaining the considerable heterogeneity of physical appearance at birth. At least 60% of the variation of birthweight could be attributed to "environmental" factors and only a small proportion to genetic or chromosomal factors (12). Indeed, many small-for-date newborn infants show clinical and biochemical features indicating intrauterine malnutrition. Clinical observations, supported by measurements of subcutaneous fat thickness (13), ponderal or anthropometric indices (14-16), and body composition (17,18), point to a majority of SGA babies being malnourished in utero (19). At birth they also present biochemical abnormalities which are characteristic of protein malnutrition, such as changes in serum and urine amino acid patterns (20), de-
creased levels of total serum protein (20), and retinol-binding protein (21) concentrations. If those infants with congenital malformations are excluded, birth can be seen to release many SGA babies from a nutritionally inadequate "environment" caused either by maternal malnutrition or impaired utero-placental blood flow. We shall discuss how the postnatal period should provide the necessary opportunity to recover the growth deficit attributed to those "environmental" factors. We will consider the nutritional problems encountered during three separate periods: the perinatal period with the adaptations to the extrauterine environment; the neonatal period, characterized by its increased nutrient requirements; and finally, the period of catch-up growth.

EXTRAUTERINE ADAPTATION

The major perinatal sequelae of intrauterine growth retardation resulting from impairment of nutrient flow from mother to fetus include low birth weight, hypoglycemia, polycythemia, and birth asphyxia. Therefore, during the period of adaptation to extrauterine life, nutritional policies should be guided by the following aims:

1. to restore normal glucose homeostasis;
2. to control hyperviscosity resulting from polycythemia;
3. to avoid aggravating complications induced by birth asphyxia; and
4. to favor early feeding.

The appropriate-for-gestational age term neonate can remain euglycemic despite a prolonged initial fast, thanks to hepatic gluconeogenesis. The high incidence of hypoglycemia reported in the IUGR infant (22) is probably related to the combined influence of depleted liver glycogen content, increased substrate utilization, and depressed enzymatic activity necessary for gluconeogenesis (23). As these infants are also hypoketonemic (24), it is thought that the low rate of gluconeogenesis could be secondary to reduced lipolysis (25) of small endogenous fat depots and a low rate of fatty acid oxidation (25). Indeed, oral or intravenous administration of triglycerides has been shown to cause a hyperglycemic response in hypoglycemic SGA infants (26,27) by increasing the production of glucose (27). The combination of low glucose with low levels of ketones is potentially deleterious for the brain, which has elevated energy requirements during the neonatal period (28,29). These metabolic consequences of IUGR stress the importance of early feeding.

More recently, research efforts have been directed towards the effect of medium-chain triglyceride (MCT:C6:0-C12:0) feeding on glucose homeostasis. The MCT are more efficient than long-chain triglycerides in correcting fasting-induced hypoglycemia (30). The MCT yield more ketone bodies than long-chain fatty acids (31) and can sustain an active gluconeogenesis (30). Feeding an MCT formula produces a blood ketone body concentration comparable to that of term infants who have been breast-fed (32). Ketone bodies may be particularly important in the developing infant and it has been shown in the newborn that acetoacetate and β-hydroxybutyrate
are readily oxidized (33) and serve as key substrates for lipogenesis in the brain (34). This situation is quite relevant in the IUGR newborn, since high concentrations of ketone bodies could decrease the oxidation of glucose in the peripheral tissues, and thus contribute to glucose sparing (30). Therefore, during the first hours of extrauterine adaptation, when maternal milk production is not yet initiated, the early feeding of an MCT-rich solution to the hypoglycemic growth-retarded newborn can be an effective adjunct to the rapid intravenous correction of the glucose homeostasis.

Because of their rapid portal absorption and hepatic oxidation, MCT have been added to several infant formulas. Although oxidation of lipids and synthesis of ketone bodies may be enhanced, the appropriate quantity of MCT in infant formulas has not been clearly established. Storage of medium-chain triglycerides in adipose tissue of orally fed infants has been recently demonstrated (35). Figure 1 shows that in infants fed ad libitum, dietary fat is a major determinant of adipose tissue composition, confirming the saying: "You are what you eat." Furthermore, under normal nutritional conditions, MCT are not used solely as a source of energy but can also be re-esterified or serve for chain elongation before being deposited in fat stores. Those infants receiving formulas with higher MCT content had up to 10% of medium-chain fatty acids in their adipose tissue (35). The long-term physiological effects of MCT-rich diets should be carefully evaluated, as dietary lipids are known to influence both cellular properties (36) and membrane structure (37).

IUGR neonates have a high incidence of chronic fetal distress and birth asphyxia (38). Therefore, the early feeding of these infants should be initiated with caution. Erythropoiesis is stimulated by chronic fetal distress with hypoxia. This results in an

![Graph showing adipose content vs. dietary content](image-url)

**FIG. 1.** Significant linear regressions are plotted for individual fatty acids, between the content of medium chain fatty acids (C8:0, C10:0, C12:0) and long-chain fatty acids (C14:0, C18:1, C18:2) in commonly used sources of diet (mother’s milk, formulas) on adipose tissue content of these fatty acids. For C18:2, \( Y = 0.75X + 1.8, n = 29, r = 0.87 \); for C18:1, \( Y = 0.74X + 10.9, n = 29, r = 0.93 \); for C14:0, \( Y = 0.41X + 3.6, n = 29, r = 0.71 \); for C12:0, \( Y = 0.53X - 3.5, n = 29, r = 0.95 \); for C10:0, \( Y = 0.1X + 0.5, n = 29, r = 0.8 \); for C8:0, \( Y = 0.08X + 0.2, n = 29, r = 0.9 \). (From ref. 35.)
increase in fetal hemoglobin synthesis (39). Many SGA infants are polycythemic (38,40), and polycythemia is generally associated with hyperviscosity (41), resulting in a sluggish gastrointestinal blood flow. Gastrointestinal disturbances may be apparent in the form of feeding intolerance and in the more severe cases of necrotizing enterocolitis (NEC) (42). Necrotizing enterocolitis is characterized by signs of sepsis in addition to bile-stained vomiting, bloody stools, intestinal perforation, peritonitis, and shock (43). Fetal hypoxia will also result in decreased gastrointestinal perfusion, and again cause increased vulnerability to NEC (44). It was thought that delaying oral-feeding might reduce the incidence of NEC (45,46). Although enteral substrates may be important in the development of NEC, studies conducted in a prospective fashion have demonstrated that delaying feeding failed to prevent necrotizing enterocolitis (47,48). Moreover, functional gut maturation is dependent on enteral substrates (49). In the animal model of NEC (50,51), fresh breast milk protected newborn rats from a similar disease (50,51). However, NEC can occur in neonates fed exclusively on human milk (52,53).

Therefore, during this period of extrauterine adaptation a slowly progressive feeding schedule should be advocated (49,54). When breast milk is not available, early enteral feeding should be initiated with a low volume of low osmolar, medium-chain triglyceride containing formula (48). During this early stage of feeding it is not so much the global energy intake which is to be emphasized, but the quality of available substrate.

INCREASED NUTRIENT REQUIREMENTS

The effects of intrauterine malnutrition on gastrointestinal development in humans have not been investigated. Before increasing the nutrient intake in growth-retarded infants up to full feedings, one should be aware that neonatal animal data suggest subnormal gastrointestinal function as the result of intrauterine malnutrition. A decrease in both intestinal and pancreatic weight secondary to a reduction in the number of cells has been documented in rats undernourished during fetal life (55,56), along with a reduction in total pancreatic enzymes (55). In humans, malnutrition in early infancy has been associated with atrophy of the pancreas and intestinal mucosa in fatal cases of kwashiorkor (57). On the other hand, it has also been shown (58) that there was comparable pancreatic endocrine activity in 48-hr-old SGA and appropriate-for-gestational-age (AGA) infants after an oral glucose load and protein stimulation.

A quantitative evaluation of the energy metabolism of IUGR low birthweight infants has been carried out (29). By combining energy and macronutrient balances with open-circuit indirect calorimetry, the absorption, utilization, and storage of energy and macronutrients were compared between SGA and AGA low birthweight infants. Fourteen studies were performed in six SGA infants (mean ± SEM birthweight: 1.12 ± 0.03 kg; gestational age: 33.1 ± 0.3 weeks; postnatal age: 26 ± 3 days). Twenty-two studies were undertaken in 13 AGA infants (birthweight: 1.15 ± 0.04 kg; gestational age: 29.3 ± 0.4 weeks; postnatal age: 21 ± 2 days). The
TABLE 1. Macronutrient intake and partition of losses in excretion

<table>
<thead>
<tr>
<th>Intake</th>
<th>IUGR</th>
<th>AGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat</td>
<td>8.0 ± 0.1</td>
<td>7.5 ± 0.2</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>16.0 ± 0.2</td>
<td>15.2 ± 0.4</td>
</tr>
<tr>
<td>Protein</td>
<td>3.3 ± 0.1</td>
<td>3.2 ± 0.1</td>
</tr>
<tr>
<td>Energy (kcal/kg-day)</td>
<td>156 ± 2</td>
<td>149 ± 4</td>
</tr>
<tr>
<td>Energy (kJ/kg-day)</td>
<td>651 ± 9</td>
<td>621 ± 16</td>
</tr>
<tr>
<td>Losses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stool</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat</td>
<td>2.5 ± 0.3</td>
<td>1.5 ± 0.1*</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>0.05 ± 0.01</td>
<td>0.05 ± 0.02</td>
</tr>
<tr>
<td>Protein</td>
<td>1.1 ± 0.1</td>
<td>0.55 ± 0.05*</td>
</tr>
<tr>
<td>Urine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>0.10 ± 0.01</td>
<td>0.10 ± 0.01</td>
</tr>
<tr>
<td>Protein</td>
<td>0.73 ± 0.04</td>
<td>0.73 ± 0.03</td>
</tr>
<tr>
<td>Energy (kcal/kg-day)</td>
<td>30 ± 3</td>
<td>18 ± 2*</td>
</tr>
<tr>
<td>Energy (kJ/kg-day)</td>
<td>125 ± 11</td>
<td>76 ± 6*</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SEM.
IUGR, intrauterine growth retardation; AGA, appropriate-for-gestational-age
*p < 0.05.
Adapted from ref. 29.

Routine feeding schedule provided SGA and AGA infants with similar volumes of long-chain triglycerides (84%) containing formula (185 ± 2 versus 180 ± 3 ml/kg-day). The comparison between macronutrient and energy intakes and the partition of losses in excretion are presented in Table 1. Macronutrient and energy utilization was determined by respiratory gas exchange measurements using the principles of indirect calorimetry. The results of macronutrient and energy utilization and deposition are presented in Table 2. The IUGR infants demonstrated different metabolic responses to the diet in nutrient absorption, energy metabolism, and newly deposited tissues.

Protein absorption was significantly lower in the IUGR infants (69 ± 3 versus 83 ± 2%). Figure 2 shows that there were increased protein losses in these infants. A lower protein digestibility has also been documented in a smaller number of comparative studies on protein turnover in IUGR and AGA low birthweight infants (59). The whole body protein turnover was 26% higher in SGA infants. In older infants treated for malnutrition, the protein turnover rate almost doubled during recovery from undernutrition (60). SGA infants show the same adaptation of their protein metabolism as they recover from intrauterine growth retardation (59). Furthermore, protein synthesis and breakdown were both significantly increased in the growth-
TABLE 2. Macronutrient utilization and deposition

<table>
<thead>
<tr>
<th></th>
<th>Metabolizable intake</th>
<th>Utilization</th>
<th>Deposition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IUGR</td>
<td>AGA</td>
<td>IUGR</td>
</tr>
<tr>
<td>Fat (g/kg-day)</td>
<td>5.5 ± 0.2</td>
<td>6.0 ± 0.2</td>
<td>1.2 ± 0.3</td>
</tr>
<tr>
<td>Carbohydrate (g/kg-day)</td>
<td>15.85 ± 0.2</td>
<td>15.05 ± 0.4</td>
<td>13.2 ± 0.6</td>
</tr>
<tr>
<td>Protein (g/kg-day)</td>
<td>2.2 ± 0.1</td>
<td>2.65 ± 0.1*</td>
<td>0.73 ± 0.04</td>
</tr>
<tr>
<td>Energy (kcal/kg-day)</td>
<td>126 ± 3</td>
<td>130 ± 4</td>
<td>67 ± 1</td>
</tr>
<tr>
<td>(kJ/kg-day)</td>
<td>526 ± 10</td>
<td>545 ± 14</td>
<td>282 ± 5</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SEM.
IUGR, intrauterine growth retardation; AGA, appropriate-for-gestational-age.
Metabolizable intake: intake - losses; Deposition: metabolizable intake - utilization.
*p < 0.05.
Adapted from ref. 29.

retarded newborn infants (59), explaining the lack of difference in urinary nitrogen excretion between SGA and AGA infants (29,59). For a similar protein intake received by the SGA and AGA preterm infants (Table 1), the protein retention (as calculated from the nitrogen retention) was significantly lower in the SGA infants (Table 2). Although these protein intakes fell within requirements for IUGR infants (61) the retention (1.6 g/kg-day) fell short of intrauterine accretion rates (Fig. 3). Therefore, the published values of protein requirements (Table 3) for IUGR infants (61) might be somewhat underestimated, because of a lower than anticipated protein digestibility. However, the protein turnover data (59) show that these infants can

![Energy and macronutrient losses](image-url)
adapt to a subnormal intake by more intense reutilization of endogenous amino acids.

Fat absorption was significantly worse (69 ± 3 versus 83 ± 2%) in the SGA preterm infants (29); Fig. 2 shows the greater fat loss in these infants. Severe malabsorption of nitrogen and fat is also present in malnourished infants (63). The diminished enzymatic activities of lipase and trypsin documented in animal studies on malnutrition (64) offer a pathophysiological basis for the finding of relative fat and protein malabsorption in IUGR preterm infants. Fat oxidation was 50% higher

TABLE 3. Protein requirements for IUGR infants in the first 3 months of life

<table>
<thead>
<tr>
<th>Age (month)</th>
<th>Protein requirements (g/kg-day)</th>
<th>Protein requirements (g/100 kcal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3.2</td>
<td>2.5</td>
</tr>
<tr>
<td>1</td>
<td>2.5</td>
<td>2.0</td>
</tr>
<tr>
<td>2</td>
<td>2.2</td>
<td>1.7</td>
</tr>
<tr>
<td>3</td>
<td>1.9</td>
<td>1.5</td>
</tr>
</tbody>
</table>

IUGR, intrauterine growth retardation.
Adapted from ref. 61.
in the growth-retarded infants compared to the AGAs; however, this difference did not reach statistical significance (Table 2). Others (65,66) have documented a lower respiratory quotient in SGA infants, pre- as well as postprandially. Such a difference in metabolic response reflects a greater dependence on fat metabolism by the IUGR infant. This is confirmed by a study showing that after the oral administration of lipids, the blood concentration of ketone bodies increased by 120% in SGA infants, compared to only 40% in AGA infants (27). On the other hand, after an intravenous lipid test, significantly higher concentrations of triglycerides and free fatty acids were found in IUGR infants (67). These data have been interpreted as showing a limited capacity of the IUGR infant to hydrolyze triglycerides and utilize the fatty acids. However, the poor utilization of intravenously administered lipids is contrary to the indirect evidence of greater oxidation documented in the orally fed IUGR infants. Therefore, the prolonged elevation of free fatty acid levels (67) may rather be evidence of a low free fatty acid uptake by the reduced mass of adipose tissue in the growth-retarded infant. The higher fatty acid oxidation of the orally fed IUGR infant suggests a higher substrate demand in order to cover the increased energy expenditure found in these babies.

The fecal losses of carbohydrate were similar in IUGR and AGA infants (Table 1). However, a significant impairment of D-xylose absorption is present in growth-retarded infants over the first few weeks of postnatal life (68). Moreover, the small intestine of rats with experimentally induced intrauterine growth retardation has a reduced lactase content compared with appropriately grown controls (69). With the hydrogen breath test (70) it has been shown that a substantial proportion of lactose escapes absorption in the small intestine before being fermented by colonic bacteria. During fermentation this carbohydrate would be converted into rapidly absorbed volatile fatty acids (71). This process could explain the low fecal recovery of carbohydrate as shown in Table 1. The relative functional importance of this carbohydrate salvaging mechanism remains to be explored for different sources of carbohydrates (lactose, glucose, sucrose, dextrin-maltose) in IUGR as well as AGA newborn infants.

Delayed bone mineralization has been found in SGA infants (72). In one study bone mineral content was found to be significantly reduced at birth in term growth-retarded infants compared with term AGA infants (73). During the 12 weeks of that study, the postnatal increase in bone mineral content of the SGA infants lagged significantly behind that of AGA infants. This delayed skeletal maturation might be responsible for the deficit in height described in IUGR infants at follow-up through adolescence (3). On the other hand, preterm SGA infants do not have a delayed bone mineral content compared to preterm AGA infants (73,74). It has been suggested that neither hepatic hydroxylation of vitamin D nor renal hydroxylation of 25-hydroxyvitamin D is delayed in SGA infants (73). Malabsorption of fat has been shown to impede calcium absorption (75). Several pathophysiological explanations have been suggested for this controversial observation (75). Long-chain saturated fatty acids form insoluble soaps with calcium (Ca) in the intestine, preventing its absorption, an observation supported by the finding that MCT have been shown to im-
prove fat as well as Ca absorption in low birthweight infants (76,77). On the other hand, a decrease in fat absorption with increasing Ca intake could take place because of an inhibition of lipase activity. Thus it seems possible that a poor mineral balance, associated with the fat malabsorption described in the IUGR infants, could play a role in poor bone growth.

The relative hypermetabolism of malnourished newborns has been documented by a number of authors (29,78–80). Oxygen consumption was found to be significantly higher (9.37 ± 0.2 versus 8.66 ± 0.1 ml/kg-day), and the global energy expenditure (Table 2) as well as the resting preprandial metabolic rate (57.6 ± 1.0 versus 54.2 ± 1.3 kcal/kg-day; or 241 ± 4 versus 226 ± 5 kJ/kg-day) were increased in the growth-retarded infants (29). Age, weight, relative organ size, growth rate, energy intake, thermal environment, and activity are the major factors influencing metabolic rate (81). The hypermetabolism of SGA infants is unlikely to be due to an increase in the energy cost of activity since the higher energy expenditure persisted under resting conditions. When attempting to predict the energy expenditure of an individual from clinical variables, metabolic rate is best correlated with the active cell mass (82). Thus the hypermetabolic undergrown baby appears to have a higher ratio of metabolically active cell mass to total body mass which is consistent with his longer gestation (78). New tissue deposition is an energy-consuming process (Fig. 4), and with increasing energy intake, the energy cost of tissue synthesis also increases, as does the metabolic rate. Since the energy cost of tissue synthesis is measured as part of the global energy expenditure, the faster growth rate (catch-up growth) exhibited by some IUGR infants could explain part of their relative hypermetabolism. From postmortem analysis of organ size in growth-retarded and normal

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**FIG. 4.** Diagrammatic representation of the partition of energy metabolism in growing infants cared for under resting conditions in a thermoneutral environment. Energy cost of tissue synthesis is measured as part of the global energy expenditure (metabolic rate). With increasing energy intake the weight gain is greater, but the energy cost of tissue synthesis increases and so does the metabolic rate. Therefore the catch-up growth of IUGR infants could explain part of their relative hypermetabolism. (From ref. 81.)
infants (83) it is apparent that the heavier brain weight of SGA infants is the single major organ size difference. As the brain has the greatest energy requirement of all organs during the neonatal period (28), it has been speculated that the larger brain size to body weight ratio of IUGR infants could account for their hypermetabolism (29,78).

A rise in basal metabolic rate is a well-known phenomenon during recovery from malnutrition (84). Infants with growth failure due to maternal deprivation have an increase in postprandial heat production during the recovery phase (85). This specific dynamic action or thermic effect of food was best correlated with weight gain. Furthermore, the energy cost of growth could explain part of the relative hypermetabolism, as IUGR infants often exhibit a faster growth rate or "catch-up" growth. The increased protein synthesis documented in these infants (59) could account for the higher energy expended for growth (86). Thus, the hypermetabolism of IUGR infants is probably due to two factors: higher rate of growth and larger brain size.

For a comparable volume of milk, IUGR infants have a lower storage of energy than AGA infants (Table 2). Therefore, growth-retarded infants require high-energy feedings in order to satisfy their higher metabolic rate and their increased requirement for catch-up growth.

CATCH-UP GROWTH

A considerable number of follow-up studies point to the fact that IUGR infants show an accelerated growth pattern during the first 6 months of life. From then on, their average weight and height follow a constant course along the same percentile line (2,19,87–89). Therefore, when reaching adolescence the infants born with growth retardation are, as a group, significantly smaller in weight, height, and head circumference than matched controls of normal birthweight (3). This holds true for both term and preterm IUGR infants. The "catch-up" describes the accelerated growth which follows a period of growth retardation and tends to return the infant to a normal growth trajectory. However, the means whereby SGA infants catch up are not fully understood and there seems to be a time-limited potential for catch-up growth.

Because of increased energy requirements (29), high-energy feeding is advocated as nutritional support for the growth-retarded infant. Similarly, high-energy feeding in protein-energy malnutrition produces an accelerated rate of growth (90). However, the long-term effects of such a treatment on spontaneous food intake are poorly understood. The influence of appetite control on energy intake and catch-up growth has been investigated in two groups of SGA infants with distinct etiologies: (a) in those wasted infants born with clinical evidence of intrauterine malnutrition (decreased ponderal index) (91), and (b) in a group of infants who were genetically at the bottom end of the normal range (92) (normal ponderal index). The wasted SGA infants fed *ad libitum* consumed significantly more milk per unit weight than larger babies in the first two months after birth (91). The mean weight gain per kg
and per day was significantly higher in these babies. On the other hand, in an elegant study (92), genetically growth-retarded infants fed ad libitum were randomly allocated to receive a high-energy (87 kcal/dl; 364 kJ/dl) or a standard energy formula (65 kcal/dl; 270 kJ/dl). Infants on high-energy feeds consumed lower volumes throughout the 3 months of the study. Thanks to the increased energy density of the feeds, the metabolizable energy intake of these infants was significantly greater in the early weeks of the study. After 2 months of age, energy intakes were similar in both groups. The high-energy formula group gained weight at a faster rate than did the other group. These data demonstrate that the hypothalamic center for appetite control is functional in the earliest months of life. The fact that the energy intakes of the two groups were no longer different after three months offers an explanation for the limited time during which catch-up growth is to be found in IUGR infants.

SUMMARY

Intrauterine growth-retarded infants present specific postnatal metabolic and nutritional problems. They have a decreased absorption of fat and protein, hence increased energy loss in excreta. The relative hypermetabolism of these infants is associated with a larger brain size, increased fat oxidation and protein synthesis, as well as accelerated rate of growth. Unless high-energy feeding is offered in the earliest weeks of life, catch-up growth might not occur. Breast milk should specifically be advocated when there is a risk of gastrointestinal disturbances associated with chronic fetal distress and/or asphyxia.

REFERENCES


DISCUSSION

Dr. Guesry: I enjoyed your talk very much and would like to come back to a few of the things you said. In the first place, you rightly said that we need to give more energy to the baby, but on the other hand, the feed osmolality must be low and we must avoid high-protein intakes. If you want to do all these things, you must give fat. We all know that fat is not well absorbed unless you give medium-chain triglycerides (MCT), but, and this is my second point, you raised doubts by speaking of the potential danger of deposition of MCT in adipose tissue. You also said that this deposition was mainly of C12 fatty acids and a little of C10. The MCT which are used in formulas designed for low birthweight infants are made almost exclusively from C6 to C10 fatty acids, with very little C12, unless coconut oil is used. So I am sorry that you should raise doubt about this particular aspect of formulas for premature babies, which in my view is all to the good.

Dr. Chessex: About your first comment: I think you may have misinterpreted what I said. I was specifically referring to the early period immediately after birth, at which time I think that it is very important to have low-volume feeding with a low osmolar load. Later on we must accept some compromises if we want to increase the energy intake. I specifically avoided laying down any ground rules about how much energy should be provided. Your comments about MCT are interesting. In North America MCT-containing formulas have a lot of C8 and very little C6, and some of them contain up to 20% C12, in other words, quite large amounts. I agree that it has been clearly shown that the shorter the chain-length the greater the oxidation and the less the storage, but if there are significant amounts of C12 in the formula they will appear in the tissues. My concerns are not limited to MCT. I am also concerned about excess linoleic acid or any blend of fatty acids which might change the properties of cells and cell membranes, particularly in the brain at this period of life when a lot of fat deposition is going on. It has been suggested (1) that altering the linoleic acid content of a formula produces significant changes in the erythrocyte deformability, documenting a direct effect of dietary lipid composition on cellular properties. I don’t have anything specifically against MCT, but I think their use should be limited to the early feeding period; later on, I am not sure they have much of a place. I don’t think it is important to have very sophisticated formulas after the first few weeks. Perhaps they are financially acceptable in industrialized societies, but I think they might be unnecessarily sophisticated for developing countries.

Dr. Guesry: I should like to answer your last point. We recently conducted a study with Alan Rothberg in a large maternity hospital in South Africa (2). The infants were fed with their own mother’s milk or with ordinary formula or with a special formula for low birthweight infants. The use of the low birthweight formula resulted in a reduction by 20 days (from 65 to 45 days) in the average length of stay in the nursery. This is very important in such hospitals because they often do not have enough cots for small infants.

Dr. Chessex: But afterwards, when they leave hospital, should they have to pay more for special formulas? Will the special formula influence their long-term outcome?

Dr. Senterre: I should like to return to the question of the use of MCT in SFD infants, since I am not convinced by your arguments for excluding them. From what I understood you to say, you feel that they should be excluded because you have shown that they are incorporated in the fat deposited by infants fed with MCT-containing formulas. But the absolute level of
incorporation is bound to be low. A proportion of ingested MCT are indeed elongated and incorporated in depot fat; the remainder, say, 60%, are readily oxidized, as has been shown with stable isotope work (3). There will be much greater incorporation of C18:2, for example, so why not exclude that? On the other hand, there are a lot of advantages in giving a formula containing about 40% MCT. It improves fat and calcium absorption and leads to better nitrogen retention for the same energy intake. So there are a lot of advantages in using such formulas and I am personally in favor of them. For obtaining a good fat absorption, the alternative is to use formulas with fat containing high levels of polyunsaturated fatty acids and/or high lauric and myristic acid levels. This would be worse than MCT in my opinion.

Dr. Chessex: My response is that you have seen only the mean values for the data; it is important to note that MCT deposition is much greater in infants who are growing faster, as it is related to weight gain. Also, with reference to your remarks about MCT oxidation, I should say that most of the work on this has been in rats. Guy Putet did a study a few years ago (4) which showed a much lower rate of oxidation. I am concerned that oxidation is not as great as we have thought, particularly in rapidly growing infants, and this obviously applies to SGA infants. In relation to your comments about formulas with high linoleic acid content, I agree entirely. It is just a question of balance. I believe that the use of formulas with modest amounts of MCT has a place in the early management but I don’t think they should be used later on.

Dr. Marini: I think the situation with regard to MCT is still controversial. For example, there are two papers showing no improvement in growth in preterm infants fed MCT formulas (5). In the second place, Tibor Heim has shown differences in plasma concentrations of cholesterol and triglyceride in infants fed with MCT formulas (6). I should say, however, that we have been unable to confirm this finding. Finally, a more general point: When you change dietary fat composition, tissue fat changes rapidly. Thus I am not too concerned about the possible long-term effects of MCT incorporation.

Dr. Chessex: In the adult it takes about 3 years to change the fat composition in adipose tissue (7). But in the infant it takes about 6 weeks. We have confirmed this in biopsies taken at fortuitous surgery. However, 6 weeks is quite a long time when the brain is growing rapidly and accumulating lipids.

Dr. Guesry: One short point about your last statement concerning the composition of the brain: It has been shown (8) that the main fat which is incorporated in the brain is docosahexaenoic acid, and only about one-third of this is derived from diet. The rest of the fatty acids deposited in the brain are synthesized.

Dr. Bracci: There is another point we haven’t considered in relation to early diet in SFD infants. These infants must be considered to have some degree of immunologic depression; for example, there are data which show depression of T-cell function and phagocytosis. Thus they are at risk of infection and we may lose some of them for this reason in the early weeks. I think therefore that the value of the protective properties of human milk should not entirely give way to nutritional considerations. I would be in favor of human milk with nutritional supplementation.

Dr. Priolisi: To follow that, I should like your comment on studies by Räähä’s group on very low birthweight infants fed at three different levels of protein intakes: 2.92 g/kg/day from human milk, 3.22 and 4.06 g/kg/day from formula. The increase in protein intake was accompanied by an increased level of serum total α-amino-nitrogen concentration, a concomitant decrease in the intraluminal bile acid concentration. This is an indirect evidence of decreased bile flow in VLBW on excessive oral protein intake (9).
Dr. Senterre: It is well-known that there is a positive relationship between plasma amino acid concentration and protein intake, but this results in an increase in the amino acid supply to the cells and increased protein anabolism, which is just what we want. As to the effect on bile acid production, I accept that there is indeed a correlation between the serum alpha amino nitrogen and serum bile acid concentration; however, the correlation is not linear. Thus, if you increase protein intake by 50% from 2 to 3 g/kg daily, which is a big increase, serum bile acid concentration remains low. Although we know that infants fed on TPN with high methionine intakes may get cholestasis, there is no justification for extrapolating from Raiha's data that if we give a 3 g/kg protein intake enterally in these babies we shall then get biliary stasis. I should also like to comment on Dr. Chessex's protein turnover data. You told us that protein turnover, both synthesis and breakdown, was increased in SFD babies. But you also said that you saw no increase in urinary nitrogen excretion. Since recycling of amino acids is never 100%, a higher protein turnover is bound to be associated with increased urinary nitrogen excretion.

Dr. Chessex: How then would you explain the fact that we had exactly the same nitrogen excretion in our two groups? Do you think it was because we had a sufficient protein intake in both groups, so that they did not have to increase their protein turnover?

Dr. Senterre: No. I think urinary nitrogen excretion in those babies was chiefly related to nitrogen utilization in new tissue synthesis rather than to protein turnover. You showed that your SFD babies were growing faster than preterm infants, especially in the first 3 weeks of life, so nitrogen retention and new tissue synthesis were important. Thus they used their amino acid pool for synthesis, so blood urea nitrogen and excretion decreased. On the other hand, I did not understand why, when you gave too much energy, the energy cost of growth increased so much when energy stores were only increasing slowly.

Dr. Chessex: Brooke found the same thing (10). There must be a point at which you are relatively efficient in relation to the amount of the energy intake and the cost of depositing that energy. Above that point there will be an increase in the energy cost of growth.

Dr. Senterre: I agree that if you push in too much energy you don't see a proportionate increase in energy deposition because the metabolic rate is increased. But to my mind this does not mean that the energy cost of growth is increased; it means that you are wasting energy in other metabolic pathways.

Dr. Chessex: However, the way those tissue synthesis data were derived was by measuring the difference between pre- and postprandial energy expenditures. The postprandial energy expenditure increases with energy intake and with weight as shown previously in numerous studies by Krieger (11), Brooke (12), and Ashworth (13). I accept that this is partly due to energy wasting in other pathways, as in brown fat, for instance. However, during those studies we found no change in deep colonic temperature and mean skin temperature as could be expected if brown fat was active in eliminating excess energy as heat. We have recently repeated some of the experiments during TPN and showed clearly that just by changing substrates—without changing overall energy intake—there was an increase in deep body and subscapular temperature, which is an indirect sign of brown fat activity.

Dr. Pearse: When we tried to determine the energy cost of growth using simultaneous direct and indirect calorimetry, we found that increased postprandial metabolism (specific dynamic action) in SFD infants but not in well-fed appropriate-for-gestation infants. I don't know what this means, but we know that SFD babies tend to appear hungry and much of the original work on specific dynamic action was in malnourished children.

Dr. Chessex: We did find specific dynamic action in appropriate-for-gestation infants, both
in the study I have described here and also in numerous other studies, so I cannot explain your findings.

Dr. Toubas: What about heat loss in these babies? An SFD infant must have a larger body surface area than an appropriate-for-gestation infant of similar weight. The infant will lose more heat through the skin. Should we thus be giving more fat to increase subcutaneous fat and thermal insulation?

Dr. Chessex: The babies in our study had a minimal heat loss via this route since they were in a neutral thermal environment. Indeed, the adequate provision of substrate ensures that thermoregulation is more readily achieved. This is why at the beginning I stated that we should try when possible to achieve nutritional accretion before birth.

Dr. Villar: I should like to make a comment on another matter. I do not think one should regard the SGA population as homogeneous. If you look at SFD infants of the same birth-weight but different fat and body length, you find that they have quite different ad libitum intakes; some for example will eat more than others, some will have a preference for a higher glucose intake. We should be looking at subgroups of SFD infants and not lumping them all together. I also have a question. We have been looking at tryptophan concentration in human milk in a population with a low tryptophan intake, and it occurs to me that this could reduce appetite and change sleeping patterns by increasing the synthesis of serotonin in the brain. There are data from adults which suggest that alterations in appetite and sleep can occur when the ratio of tryptophan to the other large neutral amino acids (LNAA) is changed. Do you have any experience or views on the effect of tryptophan ratios on appetite in SGA infants?

Dr. Chessex: No, I don’t, but it is an interesting question.

Dr. Guesry: We have been working on this subject for 5 years. It originates from studies by Wurtman (14) at M.I.T. who showed competition between tryptophan and the other LNAA in crossing the blood-brain barrier. If you give tryptophan together with a protein meal you don’t get any effect, but if you give it alone with carbohydrates (which increase the uptake of LNAA into muscle) you find a doubling of the tryptophan:LNAA ratio entering the brain. This increases serotonin synthesis and reduces appetite.

Dr. Senterre: Some SFD infants do not show adequate catch-up growth, and I think in these cases the problem must lie in regulation by the various growth factors. It was shown about 10 years ago (15) that SFD babies who were growing fast had much higher insulin levels than ones who were not growing, or were growing slowly. I think it is important during the first weeks of life to try to promote growth by increasing insulin secretion, which can be done by giving a relatively high protein intake, especially if the protein contains appreciable amounts of the branched chain amino acids (and also by giving carbohydrates, of course). Thus I feel that it is important to supplement the diets of SFD babies with more protein, or with sucrose, but not with additional fat.

Dr. Chessex: There have been other data documenting a linear correlation between growth rate and plasma insulin, metabolic rate and weight gain, as well as metabolic rate and insulin (16). It seems possible that it could answer the question about what determines the plateauing of catch-up growth which is seen after a while. Could this phenomenon be due to a tailing-off of insulin response? However, there is the usual question of which is the cart and which is the horse.

Dr. Villar: If you give ad libitum feeds to infants of diabetic mothers, who have high plasma insulin concentrations, these infants will have lower glucose intake. We offered, in a preliminary study, feeds of 5%, 10%, and 20% glucose ad libitum to such infants and there was a tendency among those with high insulin levels to prefer the 5% feed. This could be related to what I was saying about serotonin. If you have high insulin concentrations in plasma
you will increase transport of large neutral amino acids and, more proportionally, tryptophan, into the brain. You thus increase serotonin production, which will reduce appetite. I accept that insulin is a growth hormone, but in my opinion it is not the increase in insulin which makes you grow more, but the increase of substrate which stimulates the increase in insulin release.

Dr. Senterre: I don't think it is as straightforward as that. Infants of diabetic mothers will probably not have had IUGR; in fact they are likely to have macrosomia, so they are not comparable. We are dealing with babies in whom we wish to promote growth, and in such infants an infusion of insulin could be a way to achieve this. Also, you spoke about ad libitum feeding, but very small-for-dates infants cannot be fed ad libitum—they must be tube-fed, so we have to choose their energy intakes for them, and under these conditions it is likely that we shall get it wrong in some of them.

Dr. Girard: The correlation between plasma insulin and growth cannot take into account variations in tissue sensitivity to insulin. Take an obese adult, for example: He will have very high plasma insulin but his tissues will be quite insensitive. There is very little information about change in insulin-sensitivity in relation to growth or increase in body weight, so I think it is too naive to claim that a correlation between plasma insulin and growth means that the growth is due to the increased insulin.

Dr. Chessex: It is of interest that some SGA babies could have increased insulin receptors (17).

Dr. Girard: In obese diabetic adults there are sometimes a normal number of insulin receptors per cell but the tissues are insensitive to insulin. Although the binding to its receptor is the first step in insulin action, there are intracellular steps which could also be affected and responsible for insulin resistance. The exploration of insulin sensitivity in newborn babies with IUGR and during catch-up growth could be a fruitful field of study.

REFERENCES


