Nutrient and metabolic needs of the fetus and very small infant: a comparative approach
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Introduction
Optimal nutrition of extremely low birth weight (ELBW) and very low birth weight (VLBW) infants must provide for unique and changing requirements for energy utilization and growth of body components and proportions to mimic those of normal intrauterine growth. Normal intrauterine growth rate is an accepted current goal for these infants [1]. Such a goal is not easily or often met, however, even today with attempts at more aggressive feeding of such infants and the use of specialized intravenous and enteral nutrient products. It may be that extremely preterm birth produces insurmountable impediments to growth. These would include gravity, low humidity, low temperature, tactile pressure, breathing, peristalsis, muscle contractions, pathophysiological processes such as hypoxia and acidosis, diseases such as sepsis, medical/surgical treatments and stresses, and so on. Furthermore, many of these infants are already significantly growth-restricted at birth [2]. Such growth restriction usually results from insufficient placental transfer of nutrients to the fetus [3,3], as well as metabolic and hormonal adaptations in the fetus that act to substitute a slower rate of growth to meet the decreased nutrient supply [S]. So successful is this adaptation that further adaptation over considerable time is required before growth can resume [6,7]. In addition, most of these infants are simply not fed enough to meet the nutrient requirements for energy utilization and growth [8]. The reasons for this are many. There are real problems such as the relatively frequent occurrence of marked pathophysiology including hypoxia and acidosis, diseases such as sepsis, and pharmacological treatments such as steroids for prevention and/or treatment of chronic lung disease. There is also the fear among physicians and nurses that aggressive feeding will produce pathology — principally necrotizing enterocolitis (NEC), but also abnormal plasma concentrations of amino acids, fatty acids, hydrogen ion, and ammonia — which might prove toxic, before normalization of energy requirements and growth are achieved. There also appears to be a general reluctance among physicians caring for these infants to provide the necessary nutrients at rates that are needed for growth as well as for energy utilization. Such reluctance may stem from uncertain knowledge of the energy and protein requirements for growth that these infants need.

Methods to measure fetal nutrition
How does one know the necessary requirements for nutrient supply to ELBW and VLBW infants, and how does one know the metabolic capacities of these infants to process these nutrients for effective energy utilization and growth? Several experimental approaches have been tried [9]. One approach involves estimating neonatal nutrition by measurement of the normal fetal accretion rates of body nutrient components in utero. Although such estimates provide minimum amounts of nutrients necessary for body structure, they do not include the nutrient requirements involved in metabolism (e.g. for oxidation and energy production). A second approach involves quantifying the normal net uptake rate of nutrients by the fetus from the placenta via the umbilical circulation. This measurement more closely approximates the fetal requirements for nutrient accretion and for net utilization, but does not distinguish between these rates and does not include fetal contributions. A third approach involves the use of tracers of nutrient substrates as well as measurement of net uptake of substrates by the fetus to quantify normal rates of fetal nutrient substrate utilization and turnover. The difference between utilization and net uptake rates determines fetal contributions such as amino acid production and glucogenesis, as well as knowledge of how nutrients are used for oxidative and non-oxidative pathways, including conversion to storage products and tissue accretion. These methods require the use of large-animal models that have rates of fetal growth similar to that of human fetuses, and the

Abbreviations used: ELBW, extremely low birth weight; VLBW, very low birth weight; LCPUFA, long-chain polyunsaturated fatty acids; NEC, necrotizing enterocolitis.
GLUCOSE

Glucose is a principal energy source for the fetus and neonate. At term, the fetal sheep consumes 4–5 mg/min per kg of glucose [10], but at 50% of term gestation, the fetus consumes nearly twice this amount, 8–9 mg/min per kg [11]. Growing preterm infants who are fed fortified premature formula receive 6.7–7.4 mg/min per kg as glucose derived from lactose and glucose polymers. The larger brain of the early fetus relative to body size may account for some of this increased glucose requirement [12]. Glucose tracer studies show that over relatively short 2-h periods, approximately half of this glucose is used for oxidation and half for conversion to storage products such as glycogen and lipid and to carbon in protein structures [13]. ELBW and VLBW infants are often given less than this amount of glucose in the first days of life. Later, much more usually is provided, but rates of glucose infusion above 8–11 mg/min per kg frequently produce marked hyperglycemia [14]. The reason for frequent hyperglycemia among ELBW and VLBW infants is not known, but seems to be a combination of excessive glucose supply plus a limited secretion of insulin [15,16]. The latter is characteristic of all mammalian fetuses who demonstrate only limited insulin secretion in response to glucose and other secretagogues until after term birth [17]. Higher infusion rates of glucose, even when hyperglycemia is less of a problem, direct glucose carbon, primarily via glycerol production, into lipid production. This is energy-inefficient, produces excessive CO₂, and leads to fatty deposits in the heart and liver as well as in white adipose tissue. Such processes are promoted by insulin infusion, which is effective in promoting glucose utilization in ELBW and VLBW infants [18], as it does in the mid-gestation fetal sheep [19].

There is no justification, therefore, for providing more than 8–10 mg/min per kg of glucose in any form, with or without exogenous insulin, for normal metabolism of glucose, energy production, or to support normal rates of fetal body growth (including tissue energy stores).

LIPID

Fat accretion in the human is greater than that of all other mammals (except for the aquatic mammals) [20]. Beginning at about 20 weeks of gestation, the average accumulation of fat during the second half of gestation is about 3.5 g/kg per day [21]. This occurs while glucose uptake is decreasing on a weight-specific basis, and includes considerable fatty acid transport capacity of the placenta [22]. These observations also indicate that giving more glucose and lipid to a newborn of similar early gestational age will probably produce a fatter infant. Such information argues that glucose supply in excess of 8–10 mg/min per kg combined with lipid supply in excess of 3.5 g/kg per day is unnecessary. For the ELBW infant, such high rates of fat intake might be further undesirable, because at very early gestational ages (e.g. less than 28–30 weeks) fat accumulation, and thus requirements, are much lower [21]. The human placenta also readily transfers essential fatty acids and their long-chain polyunsaturated (LCPUFA) derivatives, in the order of docosahexanoic > α-linolenic > linoleic > oleic > arachidonic acid [22]. It appears from these and other studies of preterm infants using stable isotopes to estimate the synthesis of LCPUFA that the fetus and preterm infant are reasonably competent to synthesize their requirement of arachidonic acid [23]. In contrast the fetus (via placental transport) and the preterm neonate (via its intravenous and enteral diets) are more dependent on exogenous supply for their requirement of docosahexanoic acid. These estimates indicate that provision of these essential fatty acids and LCPUFA for ELBW and VLBW infants should be fundamental.

When energy supply is less than required, as often occurs during the first few days of life in these infants (who at that time are receiving only limited amounts of glucose) any fatty acid will be oxidized for energy production [24]. This applies to the essential fatty acids and LCPUFA as well as other fatty acids. Energy deficiency thus could lead to a deprivation of key elements for membrane and neuronal structural growth and function at a critical stage of development, particularly in the brain [24,25]. Whether or not this is reversible is not known, nor to what extent it might contribute to long-term adverse neurodevelopmental outcomes.
Energy

Energy metabolism of the human fetus is relatively constant, as it is in the experimental animal model such as the fetal sheep, at about 50 kcal/kg per day [21]. This energy requirement can be met by 5 mg/min per kg of glucose (30 kcal/kg per day) and 2 g/kg per day of lipid (20 kcal/kg per day). This energy supply also allows normal protein accretion and growth of the fetus at this early stage of development, and should provide a minimal goal for immediate energy supply after birth. Additional glucose and lipid would probably not produce a faster rate of protein accretion or growth, but would lead to fat accumulation. Because fat accumulation is a normal development for the human fetus, it is reasonable to provide enough glucose and lipid for this to occur. Normal fat accretion in utero during the second half of gestation would require about 40 kcal/kg per day more than for energy metabolism, which could be met by an additional supply of 1.5 g/kg per day of lipid (15 kcal/kg per day) and 4 mg/min per kg of glucose. Based on this approach to estimate energy needs, the total glucose requirement for ELBW and VLBW infants is about 9 mg/min per kg and the total lipid requirement is 3.5 g/kg per day. At appropriate rates of protein intake, growth of ELBW and VLBW infants does not start, or reach in utero growth rates, until after this amount of energy is provided [26].

Protein

In the late-gestation fetal sheep, nitrogen accumulation (primarily in protein) plus nitrogen excretion (as urea) is about 1 g/kg per day, approximately equal to the net nitrogen uptake [27]. Assuming 6.25 g protein per g nitrogen, amino acid requirements for fetal sheep (for both protein accretion and urea excretion) would be about 6.25 g/kg per day. The fetal sheep grows about four times as fast as the human fetus (60 versus 15 g/kg per day) and has a similar protein body content (12%) [28]; thus, the minimal amino acid requirement for the human fetus would be 1.6 g/kg per day using fetal sheep requirements as guidelines.

Ziegler has estimated this requirement for human fetuses to be higher, particularly in early gestation, at about 3.6 g/kg per day [29,30]. This higher estimate is consistent with the other data in fetal sheep, which show that the fractional protein synthetic rate of the mid-gestation fetus is about three times that of the term fetus [31,32]. Thus, 23–30-week human fetuses, whether based on Ziegler’s calculations or those of experiments in mid-gestation fetal sheep, need about 3.6–4.8 g/kg per day of amino acids for normal protein synthesis. Interestingly, this is also the rate of protein supply from enriched preterm formulae or fortified human milk when ELBW and VLBW infants are growing at normal in utero growth rates.

Such estimates of amino acid or protein requirements for normal growth are far greater than that received by most ELBW and VLBW infants, often for many days and even weeks after birth [8]. Greater attention has been paid to provision of extra energy as glucose and lipid. This has led to frequently severe hyperglycemia and excessive adiposity. Excessive lipid synthesis from glucose also has been assumed to lead to excessive CO2 production, which can lead to respiratory acidosis and respiratory distress. Without appropriate protein supply, therefore, high rates of energy supply will not lead to greater protein accretion or growth of lean body mass. It is not surprising that these infants do not achieve normal in utero growth rates easily or early after birth, but instead become fat.

Conclusions

Studies in the experimental model of the fetal sheep have shown that the mid-gestation to early third trimester fetus uses about 8–10 mg/min per kg of glucose. This rate also is about the maximum rate of glucose supply that is tolerated by ELBW and VLBW human preterm infants, serving energy requirements, growth, and carbon deposition in glycogen and fat. The mid-gestation to early third trimester sheep fetus also consumes about 6.25 mg/min per kg of amino acids. When scaled to the same rate of growth of lean body mass of the early preterm human neonate, this rate is about 3.6–4.8 g/kg per day. Human studies have shown a fat deposition rate that needs about 2 g/kg per day of lipid supply (and/or synthesis). Fetal sheep studies that are consistent with measurements in preterm human neonates also define an energy requirement for metabolism of 50 kcal/kg per day. Together, these requirements support the normal in utero rate of fetal growth in humans, and interestingly, they also are the nutrient intake rates that are observed when ELBW and VLBW infants are finally growing at the normal in utero growth rate. If catch-up growth also is desired, even greater amounts of nutrients will be needed for
these growing infants. These additional nutrients should be supplied in about the same proportion of carbohydrate, lipid, and protein as the basic requirements, although an emphasis on protein seems more important, given its more direct relationship with growth of lean body mass and length. Comparative studies, therefore, provide important guidelines for the nutritional requirements of human ELBW and VLBW newborn infants.

1 Committee on Nutrition, American Academy of Pediatrics (1985) Pediatrics 75, 976

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