Can extraterine growth approximate intrauterine growth? Should it?1–3

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ABSTRACT
Most studies evaluating the growth of preterm infants use the so-called intrauterine growth curve and reference fetus as standards. These curves might not be the optimal standards, however, for several reasons. The curves were constructed from small numbers of infants with uncertainty about gestational age, reasons for preterm birth, and, for body-composition data, the reasons for the death of the infant. Second, preterm infants after birth are not comparable with fetuses, being in a completely different environment and receiving a completely different nutrition. For instance, a higher percentage of body fat in preterm infants might well be an adequate adaptation to their environment. To get preterm infants to adhere to their supposed growth curve percentile, catch-up growth is needed. Recent studies indicate that catch-up growth might be advantageous for brain development. It might at the same time increase the incidence of cardiovascular disease in later life. The use of intrauterine growth curves to evaluate postnatal growth needs a critical reevaluation. Am J Clin Nutr 2007;85(suppl):608S–13S.

KEY WORDS Intrauterine growth curves, growth, preterm infants, catch-up growth, neonatal nutrition, neonatal body composition

INTRAUTERINE GROWTH
Birth weight is one of the most important characteristics in the evaluation of the well-being of a child at birth. Weight at birth, however, not only is a reflection of the intrauterine development, but also is determined by the duration of pregnancy. This factor was recognized many years ago, and so-called intrauterine growth curves were designed where weight was plotted against duration of gestation (1–3). Some curves are, additionally, adjusted for parity and sex. One of the greatest problems in constructing intrauterine growth curves is the determination of gestational age. Most intrauterine growth curves were developed in the period before the routine use of early ultrasound scanning. Gestational age, therefore, was completely dependent on maternal history. However, even with ultrasound scanning, the variability in estimating gestational age is ≥1 wk.

A second concern regarding intrauterine growth curves is that they are constructed from infants born prematurely, whereas the reason the infant was born prematurely often is unknown. A less optimal intrauterine environment might have caused a reduction in weight gain and at the same time preterm birth. It is never possible to evaluate the intrauterine growth potential of a child born prematurely. One study estimated that up to 50% of preterm labor is associated with intrauterine growth restriction (4). Greisen et al (5), using serial ultrasound measurements, estimated that up to 40% of infants born at 28–30 wk are growth retarded.

Finally, intrauterine growth curves are constructed from cross-sectional data, whereas growth is a continuous process. When the extraterine growth curve is connected to the intrauterine curves, it does not result in a smooth curve. Whether this indicates that the intrauterine growth curve underestimates normal fetal growth is unclear. It also might be due to the use of cohorts from different areas for the intrauterine and extraterine curves. Recently, we combined birth weight data from infants of different gestational ages with postnatal growth figures from the same area in the Netherlands and observed that there was a continuous line in weight (Figure 1). Thus, the use of data from the same geographical area might be important. Length at birth gives better information on the intrauterine accretion of lean mass. Length at birth, however, is difficult to measure accurately. Lower-leg length is a good indicator for total body length and can be measured accurately. No study has measured lower-leg length in relation to gestational age, however, nor whether lower-leg length is a good indicator for intrauterine growth retardation.

The use of weight as an indicator of the condition of the newborn neglects that 2 infants with equal weight might have very different body composition. The body water content of an infant may vary from ≈80% in infants born at 28 wk to 65% in infants born at term (6). Body composition, therefore, will better reflect intrauterine growth than will body weight. The data on body composition are quite old. It will not be possible, not only for ethical constraints, to repeat the studies of Widdowson (6) that measured the body composition of deceased infants by chemical analysis. On the basis of the existing data, Ziegler (7) constructed the so-called reference fetus. All data were later reviewed by Sparks (8). The data on which the reference fetus is based, however, were constructed at a time when no attention was given to the gestational age of the infants that were included. Second, whether the death of the infants was due to factors that also cause intrauterine growth retardation is unknown.

Despite these important uncertainties, both the intrauterine growth curves and the reference fetus are generally used not only to evaluate the condition of the infant at birth, but also to evaluate...
The fetal environment therefore is completely different from the nutrition of the infants, fat becomes the major supplier of energy. After birth, when human milk becomes the sole factor. The main nutrients of the fetus are glucose, lactate, and the binding proteins, thyroxin becomes an important growth factor. The hormones that influence growth before birth are mainly insulin-like growth factor I and II (IGF-I/II), IGF binding protein 3 (IGF-BP3), and insulin. This differs from the postnatal situation, in which next to IgF-I/II and (IGF-I/II), IGF binding protein 3 (IGF-BP3), and insulin. This differs from the postnatal situation, in which next to IgF-I/II and IGF-BP3, IGF-1 and 2, and IGF-BP3 become important regulators of growth. The newborn has to defend himself or herself against infections, a situation also remarkably different from the fetal period. All these aspects indicate that preterm infants are incomparable to the fetus in utero. Using estimated intrauterine growth as a standard for extrauterine growth therefore does not seem appropriate.

Birth causes an abrupt interruption of the constant flow of nutrients and oxygen delivered by the placenta. During the first days after birth, it is hard, or quite impossible, to deliver the same flow of nutrients as during the intrauterine period. A further complication is that the exact flow of nutrients during fetal life in humans is unknown. Concentrations of nutrients in umbilical cord blood do not reflect the flux of nutrients. The exact amounts of nutrients delivered during fetal life therefore are unknown. Not only does preterm birth interrupt fetal nutrition, but in the first days after birth, body weight decreases or, at best, does not increase, whereas it could be assumed that continuation of pregnancy would have caused a continued weight gain. This decrease in weight most likely is due to a combined loss of body water and solids (12). Recent studies indicate that the degree of postnatal weight loss as well as the time to regain birth weight might have implications for later life (discussed below).

**FACTORS INFLUENCING GROWTH**

Physical growth is a complex combination of changes in weight, height, head circumference, and body composition. Growth also is a sign of development. Growth is influenced by many factors, such as genetic background, hormones, nutrition, and environment (Figure 2; 9). The hormones that influence growth before birth are mainly insulin-like growth factor I and II (IGF-I/II), IGF binding protein 3 (IGF-BP3), and insulin. This differs from the postnatal situation, in which next to IGF-I/II and the binding proteins, thyroxin becomes an important growth factor. The main nutrients of the fetus are glucose, lactate, and amino acids. After birth, when human milk becomes the sole nutrition of the infants, fat becomes the major supplier of energy. The fetal environment therefore is completely different from the situation after birth. The fetus grows in a sterile and temperature-controlled environment. After birth, the child has to regulate its own temperature, when by cord clamping the inhibition of the fetal thermostat disappears (10). When the infant is not nursed within the thermoneutral environment, extra heat production is needed to maintain body temperature. At the same time, physical changes take place that help to limit heat loss. The skin of a preterm infant matures very rapidly and at 1–2 wk after birth is not very different from that of a term infant at birth (11). This rapid skin maturation limits heat loss through evaporation. The newborn has to defend himself or herself against infections, a situation also remarkably different from the fetal period. All these aspects indicate that preterm infants are incomparable to the fetus in utero. Using estimated intrauterine growth as a standard for extrauterine growth therefore does not seem appropriate.

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**EFFECT OF EARLY POSTNATAL NUTRITION ON GROWTH AND BODY COMPOSITION AFTER BIRTH**

The rate of weight gain in preterm infants is influenced by the amount of calories given, whereas gains in length and head circumference are influenced by the amount of protein in the feeding (for review, see reference 13). Various studies have shown that not only weight gain but also body composition is influenced by the amount of calories and protein in the diet (14–16; Figure 3). Increasing energy intake from 104 to 137 kcal · kg body weight · d−1 increased the amount of fat accretion without an improved protein gain. We conducted a study in which we compared nutrition with equal protein intake (2.2 g/100 mL) but different energy density (80 compared with 67 kcal/100 mL) (17). Weight gain and the amount of protein accretion in appropriate-for-gestational-age infants did not differ significantly between the formulas. However, infants receiving the lower caloric intake had much less fat deposition. The study had to be stopped in the small-for-gestational-age infants because weight gain became almost zero in the low-energy group (Table 1 and Figure 4). Both in our study and in the studies of Kashyap et al (14, 15), it was shown that fat accretion, at the recommended intake of 120–130 kcal · kg body weight · d−1, is higher in preterm infants than in a reference fetus. Preterm infants therefore will have, at corrected term age, a higher relative fat content than do full-term infants at birth (18).

These studies only indirectly measured fat accretion. In a recent study, it was shown that not only total body fat differs between infants born prematurely and term infants; body fat distribution also differs (18). Ex-preterm infants were shown to
have more visceral fat than did term infants. Both the higher presence of fat and the different distribution of fat might be related to an increased incidence of cardiovascular disease in later life.

STUDIES IN ILL PRETERM INFANTS

Almost all studies of the effect of nutrition on growth and body composition have been conducted in stable preterm infants who did not need supplementary oxygen. Studies in very tiny infants are also scanty. A few studies were done in infants on a ventilator receiving supplementary oxygen (19–21). These studies showed no difference in oxygen consumption between ventilated and nonventilated preterm infants.

Weinstein and Oh (22) measured oxygen consumption in infants with chronic lung disease. They observed that oxygen consumption was on average 20% higher in the infants with chronic disease. These results, however, are heavily debated for methodologic problems (23). Bauer et al (24) showed that oxygen consumption was 20% higher in term infants with septicemia than in control infants. Illness therefore seems to have only a modest or no effect on energy expenditure in newborn infants.

We conducted a follow-up study of preterm infants with severe bronchopulmonary dysplasia who needed corticosteroids to be weaned from the ventilator (25). Weight and length were lower than in normal term infants during the whole study period of 3–12 mo. Girls had lower weights and lengths than did boys. Total fat and protein contents were lower in ex-preterm infants than in term infants, again with lower values for girls than for boys (Figure 5).

Whether energy and protein requirements in extremely low birth weight (ELBW) infants differ from those in very low birth weight (VLBW) infants is largely unknown. Studies conducted in ELBW infants during the phase of rapid growth, at a study weight well above 1000 g, showed no difference with the energy expenditure of infants with a birthweight of 1000–1500 g (for review, see reference 26). Data on the energy expenditure of

![FIGURE 2. Interaction between early diet and genes in defining relevant health and quality of life outcome. CHO, carbohydrates. Data are from reference 9.](image1)

![TABLE 1 Composition of the normal-energy (NE) and low-energy (LE) formulas](image2)

<table>
<thead>
<tr>
<th></th>
<th>NE formula</th>
<th>LE formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy content</td>
<td>3350</td>
<td>2810</td>
</tr>
<tr>
<td>(kJ) (kcal)</td>
<td>800 670</td>
<td></td>
</tr>
<tr>
<td>Carbohydrates (g)</td>
<td>80 65</td>
<td>65</td>
</tr>
<tr>
<td>Lactose:maltodextrins (%)</td>
<td>50:50</td>
<td>50:50</td>
</tr>
<tr>
<td>Fat (g)</td>
<td>44 35</td>
<td></td>
</tr>
<tr>
<td>Medium-chain triacylglycerols (%)</td>
<td>6 6</td>
<td></td>
</tr>
<tr>
<td>12:0 (%)</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>18:1 (%)</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>18:2 (%)</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Casein:whey (%)</td>
<td>40:60</td>
<td>40:60</td>
</tr>
</tbody>
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The NE formula provided 120 kcal · kg⁻¹ · d⁻¹; the LE formula provided 100 kcal · kg⁻¹ · d⁻¹.
ELBW infants during the first days after birth are scanty. Only one study, which used the doubly labeled water technique, has been published as an abstract (27). In that study, the energy expenditure of ELBW infants was \( \approx 80 \text{ kcal/kg/day} \) compared with \( 60 \text{ kcal/kg/day} \) in VLBW infants. These data need to be confirmed.

CATCH-UP GROWTH

Catch-up growth can be defined as a gain in weight and length greater than estimated from the intrauterine (or postnatal) growth curve. In the past, catch-up growth was advised, especially for small-for-gestational-age infants. However, because almost all preterm infants lose percentiles after birth because of the loss of body weight and regain of birth weight only 1–2 wk after birth, catch-up growth has been advised for basically all preterm infants. Brandt et al (28) showed that early enhanced nutritional intake in VLBW small-for-gestational-age infants, leading to catch-up growth, improved long-term neurodevelopmental outcome. In that study, an improved developmental outcome in infants receiving enriched nutrition during the first 3–10 d of life was found. Lucas et al (29) also showed that both mental and motor development were better in preterm infants receiving a special preterm formula with a higher protein and energy content than the standard term formula. Different studies evaluated the effect of an enriched postdischarge formula on growth and bone mineralization in preterm infants. In a small study, Bishop et al (30) found a higher weight gain and better bone mineralization in the first year of life. Chan et al (31) did not observe any effect of a postdischarge feeding. Cooke et al (32) observed no effect on weight and body composition of an enriched formula after discharge when the infants were measured at 6 mo of life.

LOW BIRTH WEIGHT, CATCH-UP GROWTH, AND CARDIOVASCULAR HEALTH AT ADULT AGE

Barker et al (33) showed in their well-known studies an inverse relation between birth weight and risk of cardiovascular disease, type II diabetes, and metabolic syndrome at adult age. Although these results have been confirmed by other studies, doubts remain (for reviews, see references 34 and 35). For instance, whether a low birth weight of individuals included in this study was due to a preterm delivery or growth retardation is unknown. Moreover, basically no information was available on the nutrition received after the first few months of life until adulthood. Although animal studies support the data of Barker, all findings
are based on epidemiologic data. Factors so far considered as confounders or still unknown factors might turn out to have a greater effect.

Frankel et al (36) related birth weight and body mass in middle age with the incidence of coronary heart disease in later life. They concluded, “the association between birthweight and risk of coronary heart disease cannot be explained by associations with childhood or adulthood socio-economic status. Nor do conventional risk factors for coronary heart disease in adulthood account for the association. However, there is an important interaction between birthweight and BMI [body mass index], such that the increased risk of coronary heart disease associated with low birthweight is restricted to people who have a high BMI in adulthood. Risk of coronary heart disease seems to be defined by the combined effect of early life and later-life exposures.” Eriksson et al (37) found evidence that the highest death rate in a cohort of men born in Helsinki in the period 1924–1933 occurred in boys who were thin at birth, but whose weight caught up, so that they had an average or above average body mass from the age of 7 y. In a more recent study, it was shown that children who showed catch-up growth between 0 and 2 y of life were fatter and had more central fat distribution at 5 y of age than did other children, both of which are risk factors for cardiovascular disease later in life (38). These studies together indicate that not only low birth weight, but also rapid catch-up growth is related to a higher incidence of cardiovascular disease in later life. A nutritional intake leading to catch-up growth therefore might be beneficial for brain development. At the same time, it might also lead to a higher incidence of cardiovascular disease in later life.

POSTNATAL MALNUTRITION

Recently, Lucas et al published several articles in which they suggested that relative undernutrition early in life in preterm infants might have beneficial effects in later life (39–42). In a first paper, they showed that preterm infants receiving banked breast milk in the early neonatal period, a nutrition considered today as insufficient to obtain adequate growth, had a lower blood pressure at 13–16 y than did infants receiving a preterm formula (39). Using the same cohort of infants, they observed a lower insulin resistance in infants who received a lower nutrient diet in early life (40). Also, a lower C-reactive protein value and ratio of LDL to HDL was observed in these infants (41). Finally, better vascular health in 13–16-y-old adolescents was found in the group with the largest weight loss after birth (42). Their last results at least need further confirmation because the physiology behind this observation is unclear. The results of the other studies of Lucas et al also need confirmation, because the group of preterm infants received a variety of feedings in the neonatal period, and the percentage of patients originally included and studied at 13–16 y of age was remarkably low.

Is it possible to answer our initial question, “Can extraterrestrial growth approximate intrauterine growth? Should it?” Unfortunately, despite the many studies conducted, too many unanswered questions remain. The data underlying the intrauterine growth curve as well as the so-called reference fetus are weak. Basically, it is impossible to use these as a gold standard. Second, preterm infants are in a completely different environment compared with the fetus and receive a very different nutrition. The higher fat accretion of preterm infants compared with term infants might well be an adaptation to extraterrestrial life, for instance to improve thermoregulation and to increase body energy stores. Preterm infants often lose weight after birth. This might have a negative effect on neurodevelopmental outcome. What the effect on physical health is in later life is unclear. The same applies to catch-up growth. Catch-up growth seems to have advantages for neurodevelopmental outcome, but might be negative for cardiovascular health.

REFERENCES


