Fluid Requirements, Water Balance, and Metabolism in Low Birthweight Infants

Jean-Léopold Micheli,* Yves Schutz, Riccardo Pfister, Bernard Laubscher, André Calame and Eric Jéquier

Department of Neonatology, and *Department of Physiology, University of Lausanne, CH-1011 Lausanne, Switzerland

Changes in Body Composition During Intrauterine and Postnatal Growth

In order to appreciate how far the measurements of total body water can help in evaluating the fluid requirements of preterm infants, it is interesting to examine the evolution of whole body composition in absolute and relative terms and to compare intrauterine to early postnatal values (Fig. 1).

Measurements of fetal body composition at various gestational ages have been published by Widdowson (1), while Fomon et al. (2,3) have compiled data on body composition for the term baby and children up to 10 years of age. In the present analysis, we have considered the data from 22 weeks gestational age up to 6 months of postnatal age.

Figure 1 shows the pattern of change in body weight, lean mass, and fat tissue during growth. Lean mass is a heterogeneous compartment, composed essentially of water, protein, glycogen, and minerals. It is apparent that there is a rapid growth in lean mass and fat weight, particularly during the intrauterine period. However, when the relative body composition values are considered, a different picture emerges. The percentage of total body water shows a substantial decrease toward the end of the gestational period. Whereas between 26 and 28 weeks the body is composed of over 90% water, 3% fat, and 9% protein, these values reach 70% to 75%, 18%, and 12%, respectively, between 38 and 40 weeks, i.e., there is an increase in relative body fat by a factor of 6 (and by a factor of less than 2 for protein) over a time span of about 13 weeks (1-3).

Since fat begins to be deposited in sizable amounts from 28 weeks of gestation onward, a part of it subcutaneously, any imbalance in energy metabolism should affect skinfold thickness (4,5).
FIG. 1. The intrauterine and postnatal time course of body composition (top) and total body water content (bottom) are shown with respect to lean body mass and fat. (Adapted from refs. 1 and 3.)

POSTNATAL CHANGES IN OXYGEN UPTAKE AND ENERGY EXPENDITURE

Energy expenditure results from oxidative metabolism of carbohydrate, fat, and protein. It is usually determined indirectly from the measurement of oxygen uptake, which rises abruptly after birth from the fetal value to approximately 7 ml/kg.min (Fig. 2). In the hours following birth, oxygen consumption declines, reaching minimum values between 2 and 12 hours. Thereafter, in parallel with the increase in feeding, oxygen consumption rises gradually to 7 to 8 ml/kg.min at 14 days (6,7). This was first established in 1915 and has been confirmed ever since (8).

One liter of oxygen uptake is equivalent to 4.8 kcal when a mixture of glucose, protein, and fat is being oxidized; it is close to 5.0 kcal when glucose represents the main metabolic fuel. During the whole period of neonatal adaptation, the daily total of energy derived from protein oxidation is low, less than 2 kcal/kg.day, and may be calculated by measuring the urinary nitrogen excretion (6,9).

Before going into more detail about water and energy metabolism during the adaptation to extrauterine life a few methodological aspects will briefly be discussed.
METHODS FOR MEASURING BODY COMPOSITION AND ENERGY METABOLISM

Stable Isotope Techniques

The clinical use of stable isotopes in pediatric nutritional and metabolic research has been extensively reviewed (10–26). Briefly, the body mass can be partitioned into fat mass and lean mass. The latter can be subdivided in protein and water (+ electrolytes) and can be investigated with the use of stable isotopes. Total body water can be measured by an isotopic dilution method using D₂O or H₂¹⁸O (27). The dynamic aspect of protein metabolism has been studied by using non-radioactive, stable ¹⁵-N or ¹³-C labeled amino acids as biological markers. This allows an estimation of whole body protein synthesis and protein breakdown. Since the formation of peptide bonds is a high-energy process, it is of interest to determine the rate of protein synthesis and the rate of energy expenditure simultaneously.

Methods of Metabolic Assessment in Infants

Certain methods can be used to assess the “real time” metabolic status in infants. These methods are based on the concept that an infant, like all other physical entities,
obeys the laws of thermodynamics: energy intake must equal energy expenditure. Thus it is possible to approach the measurement of metabolism from two different directions: first, to measure heat production by the body over time directly, and second, to measure the exchange of gases between the body and the environment, i.e., oxygen consumption and carbon dioxide production as an indirect measure of energy consumption.

**Direct Calorimetry**

Direct calorimetry measures heat production quantitatively. The energy content of foodstuffs is determined outside the body by igniting a small sample in a bomb calorimeter, consisting of a sealed chamber in a water bath, and measuring the heat of combustion as the rise in temperature of the water bath. The energy content of feces and urine can be measured the same way. Thus the metabolizable energy intake can be quantified (9).

In clinical direct calorimetry, the entire patient is enclosed in a calorimeter. This sophisticated research tool has greatly improved our understanding of the physiology of thermal balance and thermoregulation (28,29). However, as far as metabolic research is concerned, the apparatus is cumbersome and difficult to calibrate and transport. Therefore, it is of little help to the clinician and its applications are limited.

**Indirect Calorimetry**

This method avoids many of the problems associated with the direct techniques. It is basically a chemical rather than a physical method of determining heat exchange. The two methods of indirect calorimetry are the closed-circuit method and the open-circuit method, the latter being widely used in clinical physiology since it is more convenient than the closed-circuit technique (6,8,9,11,12,24,30–36).

**The Skinfold Caliper**

This device allows a “bedside” estimate of fat stores. The one used in our unit has been described previously (4,5). This instrument needed to be small and easily handled in the confined space of an incubator. To avoid the problems related to the interstitial water being forced out of the subcutaneous tissue, the caliper was designed to apply a progressive pressure on the skin. It was calibrated to allow a digital readout of the skinfold thickness as soon as the pressure reaches 360 to 400 g/cm².

**Evaporimetric Assessment of Insensible Water Loss**

Insensible water loss comprises water loss from the skin and from the respiratory tract. In many studies insensible water loss has been determined by complicated
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indirect, mostly gravimetric methods. In 1977, Hammarlund et al. (37) described a direct evaporimetric method. Briefly, the apparatus measures a vapor pressure gradient, which is proportionate to evaporative water loss on a given site. This method can be used to measure respiratory water losses and transepidermal water losses separately (38–40).

SKIN EVAPORATIVE HEAT LOSS AND ENERGY EXPENDITURE (Fig. 3)

Premature birth is accompanied by immature skin development, so the barrier to evaporative water loss is impaired. The lack of cornified epidermis and the infant’s

![Graph showing skin evaporative energy loss and energy supply](image-url)

FIG. 3. Postnatal time course of transepidermal water loss in a group of preterm infants (n = 8, 29 ± 0.4 gestational weeks, birthweight 1250 ± 210 g). The corresponding evaporative heat loss (in kcal/kg.day) are shown on the y axis at the right of the diagram. The upper part of the diagram shows how much of energy supplied by feeding is spent to cover the evaporative skin heat losses. (Adapted from ref. 39.)
large ratio of surface area to body mass result in daily evaporative losses from the skin as high as 100 ml/kg in preterm infants of ≤27 weeks gestation during the first postnatal days (37,41). These losses decrease with increasing gestational age and increasing postnatal age (37). Each milliliter of evaporated water represents a loss of 0.58 kcal.

Simultaneous determinations of skin evaporative heat loss and oxygen consumption (Fig. 3) show how much of the total energy expenditure is accounted for by transepidermal water loss. Thus attempts have been made to reduce skin water loss by applying topical agents, thereby saving energy to cover the metabolic cost of growth. The waterproofing effect of paraffin, creams, oils, and greases was examined: overall skin water loss fell by 40% to 60%. However, there was no significant difference in terms of mortality, morbidity, or weight gain or loss when compared with a control group covered with a plastic blanket (42).

**RESPIRATORY WATER LOSS**

In full-term infants on the first day after birth, the respiratory water loss constitutes approximately half of the total insensible water loss, while in the preterm infant the transepidermal water loss is predominant. In preterm infants born between 30 and 34 weeks, daily respiratory water losses of between 6 and 8 ml/kg have been measured (38). These figures are lower if there is a high humidity in the inspiratory gas mixtures (e.g., in ventilated infants).

**URINARY WATER LOSSES**

Fetal urine flow is high compared to postnatal values. During the last trimester of gestation the daily urine output of the fetus is approximately 200 ml/kg (43). Postnatally, this value decreases by a factor of 10. Beyond the postnatal transitional period, term infants produce 40 to 60 ml per kg urine daily. In premature neonates there may be a delay in the onset of postnatal diuresis, particularly in the critically ill patient with respiratory distress. A delay in diuresis, if accompanied by administration of large volumes of parenteral therapy, has been shown to be implicated in the development of symptomatic patent ductus arteriosus and (with borderline statistical significance) of necrotizing enterocolitis (44,45). "Healthy" preterm infants have a highly variable diuresis that ranges between 15 and 25 ml/kg per day (=0.7 to 2 ml/kg per hour) during the first postnatal days. Thereafter renal function adapts to the metabolic needs as in term infants (43).

**STOOL WATER LOSSES**

In our experience and in the reported values, stool water losses vary little from one child to the other, being around 5 ml/kg per day during the first week, and 10 ml/kg per day thereafter (11,12,44).
Growth during the first 2 weeks of life is characterized by large individual variations and does not follow either intrauterine or extrauterine standards. As shown in Fig. 4, there is no postnatal interruption in supine length growth,

![Graph showing growth parameters](image)

**FIG. 4.** The early postnatal growth has been studied in nine "healthy" premature infants (mean ± SD) gestational age 30 ± 1 week, birthweight 1290 ± 170g at the postnatal ages of 3, 10, and 17 days. The upper part of the figure shows that there was no halt in postnatal growth in supine length, and by the third postnatal day the infants were already in a positive nitrogen balance. The postnatal time course of body weight followed the classical pattern. It is striking to note, in the central part of the figure, how efficiently the concentration of water in the body was regulated. No change in the percent of total body water (TBW) could be shown between days 3 and 17. Skinfold thickness were measured in five different sites (biceps, triceps, quadriceps, subscapular, and abdominal). The initial decrease of skinfold thickness parallels the loss of fat. (Adapted from ref. 47.)
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FIG. 5. The energy balance is illustrated in this figure as the difference between energy intake (upper line) and energy expenditure (lower line). Around the 30th gestational week, the fetus has a daily positive energy balance of about 40 kcal/kg.day (1). A "healthy" premature infant delivered at 30 weeks has an energy balance very close to zero at the end of day 1. This energy balance increases stepwise in parallel with feeding during the first 2 weeks of life (6). This figure allows the computation of an apparent "energy balance deficit" of 180 kcal/kg at the postnatal age of 10 days. This means that, as far as energy balance is concerned, the prematurely born infant lags behind its intrauterine counterpart and has to oxidize around 20 g of fat to cover this deficit.

though the rate slows down to about half of the values observed before and after the period of adaptation to extrauterine life (46,47). It also closely follows the postnatal time course of nitrogen balance and protein gain (6,9).

Total body water measurements obtained with H$_2$O in the same subjects suggest that the normal postnatal weight loss in preterm infants is due to relative starvation rather than to dehydration and that the subsequent weight gain is the result of an increase in tissue mass rather than rehydration (27,47,48). The severity of the initial starvation is reflected by the decrease in skinfold thickness (Fig. 4) and can also be theoretically calculated via the apparent "energy balance deficit" (Fig. 5).

The increase in tissue mass during subsequent growth can be approximated as the net deposition (or gain) of protein and fat tissues. Therefore, the energy cost of growth can be assumed to be equal to the sum of the cost of protein plus fat gain. The energy required for growth can be partitioned into two components: the energy content of the tissue deposited (called retained or stored energy) and the extra energy required for the formation of new tissue (called the metabolic cost of growth). The former depends on the composition of weight gain and has been repeatedly measured in premature babies (6,9,11,12,30–32,34–36), whereas the latter is closely related to the rate of protein turnover and protein gain. However, during growth, a mixture of fat and protein is deposited simultaneously, raising the question of the in vivo value for the metabolic cost of growth. This value cannot be measured directly, but during premature infant's first postnatal weeks it can be estimated by a regression method
A "healthy" premature infant increasing his weight at a daily rate of \( \approx 15 \text{ g/kg} \) has an average gain of 2 g protein/kg and 3 g fat/kg. The metabolic cost of growth, estimated from the regression line of energy expenditure on weight gain was found to be about 1 kcal/g, which represents a significant part (\( \approx 30\% \)) of the overall energy expenditure (6,8,33,49).

According to the basic laws of thermodynamics, this energy ultimately is turned into heat. The obvious clinical question that arises immediately is whether or not more energy could be saved for growth by reducing transepidermal evaporative water losses. This hypothesis has been tested clinically (18). It appears that if preterm infants are raised in thermoneutrality the reduction in transepidermal water losses does not influence growth (hence heat production can be considered as a by-product of growth metabolism). However, if infants are exposed to a cold stress, the situation is completely different and a reduction in transepidermal water losses may contribute to a lessening of cold-induced thermogenesis and thus to an increased rate of growth (see chapter by Jequier).

**TOTAL BODY WATER, FAT STORES, AND SKINFOLD THICKNESS**

The measurement of skinfold thickness not only includes the thickness of the fat tissue, it also involves other elements of the subcutaneous tissue, the thickness of which depends on their water content (4,5). The latter varies with the hydration of the infant. The partition between these two components of skinfold thickness is possible. During approximately the first minute after the application of a Harpenden caliper there is a steady decrease in the measurement, followed by a stabilization of the observed thickness. The quantification of this decrease is called the dynamic measurement of skinfold thickness. The values of this dynamic measurement may possibly be related to total body water, but in our hands the results had poor reproducibility (4,5).

The static values of skinfold thickness, obtained after a stabilization time of approximately 1 minute, correspond more closely to the fat tissue.

Knowledge of changes in skinfold thickness is of interest in the study of nutrition and postnatal growth. The values obtained are sensitive markers of a possible deficit in energy balance, and during the first postnatal months they give an indirect index of the decrease in total body water content. A number of practical problems preclude the utilization of more sophisticated methods such as determination of body density to get this information (9,11,30–32).

**SKINFOLD THICKNESS AND ADIPOSITY INDEX**

A significant correlation between adiposity index (body mass index) and skinfold thickness has been demonstrated. The validity of this index has also been treated in children (50,51).
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FIG. 6. Pattern of changes in adiposity index from birth up to 3 years of age in the same 19 prematurely born infants shown in Fig. 8 (5). Reference values have been recalculated from longitudinal growth charts. (Adapted from refs. 34 and 39.)

By definition, appropriate for gestational age, "healthy," low birthweight, premature infants have normal attained length and weight at birth. As expected, they also have a normal adiposity index at birth. During the postnatal adaptation they lose fat and the index drops below the 50th percentile (Fig. 6). This has been independently confirmed by the observation that total body fat assessed from the sum of four skinfolds was also below the reference values in every infant studied (4,5). Therefore, both methods (i.e., the adiposity index and the sum of four skinfolds) gave consistent results: premature babies at the end of the adaptative phase to extrauterine life have less body fat than fetuses of the same gestational age.

This conclusion seems to be in disagreement with the results obtained during metabolic balance studies (8,34,35), where a greater fat deposition was observed in premature babies than in fetuses of the same gestational age (1). It should be stressed, however, that balance techniques do not measure the total amount of body fat but only give an estimate of net fat accretion. The published metabolic studies were performed at a postnatal age when premature babies had already initiated their rapid growth, so that a large fat accretion in conjunction with a low total body fat mass (i.e., smaller than fetuses of the same gestational age) is not an inconsistent finding. In addition, several studies have shown that the skinfold thickness of premature babies is greater than that of fetuses of the same weight (4,5,35,52). However, comparison of the two groups at the same body weight implies comparing premature
babies to fetuses with smaller gestational ages and therefore with a smaller total body fat. This can explain some of the apparent contradictions in the published reports.

**FOLLOW-UP OF GROWTH AND BODY COMPOSITION DURING THE FIRST 3 YEARS OF LIFE**

Appropriate for gestational age "healthy" premature infants have normal linear growth during their first 3 years of life (Fig. 7). Their body composition, however, varies substantially when compared to term newborns.

During their first 6 months of corrected age their total body water is lower than in term infants of the same corrected age. This can be assessed indirectly via the adiposity index, which increases rapidly and crosses the 50th percentile (Fig. 6). The observation that during this period the increase in adipocity is greater in premature infants than in term babies is well known to all practitioners who follow up premature infants (30–32,48,53–55). This important increase in adiposity index occurring from 40 weeks to 6 months is related to the high rate of energy intake and fat accretion in these premature infants and is accompanied by a concomitant decrease in total

![Graph showing growth and body composition](image-url)
body water (34–36). It is interesting to note that between 36 months and 2 years the infants were apparently able to control their water, energy, and protein intakes and their metabolism in such a way that their adiposity index returned to values between the 10th and the 50th percentiles.

SUMMARY AND CONCLUSIONS

Non-invasive methods, including stable isotope techniques, evaporimetry, skinfold thickness, indirect calorimetry, and nutritional balance, have shown that the dynamics of postnatal growth in preterm infants can be summarized as follows:

1. The percentage of total body water is remarkably constant during early postnatal growth in healthy preterm infants. Thus, provided sufficient protein and energy are supplied, the water requirement of the preterm infant can be estimated by adding the anticipated volumes retained for growth and the volumes needed to replace urinary, fecal, and insensible losses (see Fig. 8).

modify intakes if:
- weight loss > 10% of birthweight,
  - (increase fluids, watch glucosuria)
- infant on a ventilator (fluid reduction = 20ml/kgxd)
- weight gain during the first 3 to 4 days
  - (fluid reduction = 20ml/kgxd)
- unexplained metabolic acidosis (check ammonia, reduce protein intake, investigate metabolism)

FIG. 8. Indicative values for fluid supply in preterm infants. All these figures have to be adapted to the individual needs. The guidelines illustrated in this figure apply to "healthy" preterm infants of less than 30 gestational weeks and less than 1250 g birthweight given "optimal" energy and protein supplies. (Adapted from ref. 18.)
2. Too great a fluid intake is accompanied by an increased risk of symptomatic patent ductus arteriosus and its complications; a restriction of fluids, however, complicates the supply of energy and protein. It is worth the effort to find the right balance because premature infants are in a range of protein-energy supply where small changes in metabolism can have a significant impact on the composition of weight gain and on growth.

3. During very early postnatal growth, in part because of the high transepidermal water and evaporative heat losses and in part because of the relatively low nutritional supply, there is a dissociated balance between energy and protein metabolism. On the one hand preterm infants lose weight and fat and decrease their skinfold thickness; on the other, they are in positive nitrogen balance, they gain protein, and continue to increase their body length.

4. Insensible water loss is influenced in predictable fashion by a number of environmental factors. An increase in air humidity, as obtained by setting incubators to provide 70% relative humidity at the thermoneutral temperature and by covering the infant with a plastic heat shield, decreases transepidermal water loss substantially.

REFERENCES


**DISCUSSION**

*Dr. Salle:* You did not mention the relationship between fluid intake and bronchopulmonary dysplasia (BPD). There are many papers suggesting that high fluid intakes in the first week predispose to BPD.

*Dr. Micheli:* I agree with what you say, the total fluid supply indicated in Fig. 8 takes this risk into account (1,2).

*Dr. Vonderweid:* Could you comment on the role of reducing transepidermal water loss in the clinical setting?

*Dr. Micheli:* Attempts to reduce transepidermal water loss to very low values were made some 10 years ago by Brice, who covered babies in paraffin gel (3). A reduction in water loss was achieved but with no change in mortality or growth rate. It is difficult to cut down these losses without covering the infant with an extremely waterproof layer and this certainly interferes with nursing and with clinical observation. Equally, to give more fluids than we do at present incurs major risks. This is why in very small infants we are concerned not to push fluids too hard.

*Dr. Simmer:* How much do you think fluid loss from the respiratory tract contributes to
the overall fluid loses and do you think it varies greatly in ventilated babies compared with non-ventilated babies?

Dr. Micheli: Respiratory water loss in preterm babies accounts for about 10% to 20% of the total water loss and this has been measured by many groups. It varies a great deal according to whether the baby is intubated or not. The few studies that have measured water flux across the airways in ventilated babies indicate that there may be a net gain in water during ventilation.

Dr. Linderkamp: Several studies have shown that transepidermal water loss is higher in smaller babies than in large ones, but nevertheless we all know that even if we give the same amount of water to tiny babies and to more mature babies the tiny babies do not lose more weight during the first few days. Have you done any balance studies on whether or not the gain of water by a ventilator in tiny infants plays a major role in this or whether it is due mainly to differences in urine output?

Dr. Micheli: We have not measured water balance in ventilated babies because we don’t have the means to measure energy expenditure in such babies.

Dr. Donzelli: What is the effect of phototherapy on transepidermal losses?

Dr. Micheli: A recent publication from Uppsala (4) showed that phototherapy causes little change in transepidermal losses. This is contrary to earlier beliefs. The Uppsala figures suggest that at the most one should allow around 20 ml/kd.d extra for babies under phototherapy.

Dr. Singh: You showed that maximum weight loss in your babies is about 5% in infants of around 1200 g. In our experience it is never less than 10% and generally between 10% and 15% during the first 3 to 4 days.

Dr. Micheli: Weight loss is influenced by fluid intake, so the amounts lost in the first few days will depend on the habitual fluid intake practices of the particular unit (2).

Dr. Singh: It is desirable to include weight loss as an important factor in assessing fluid intake.

Dr. Micheli: The problem is that you cannot wait until the next day to give orders for fluids. We, like most people, weigh our babies once a day and this certainly gives some feedback on fluid intakes but we cannot anticipate tomorrow’s weight as a guide for today’s fluid orders. Thus some guidelines may be helpful (Fig. 8) as long as the figures are adopted to individual needs.

Dr. Putet: You choose to use catecholamines rather than fluid infusions to maintain blood pressure. What are the consequences of dobutamine administration on energy expenditure?

Dr. Micheli: We have measured catecholamine excretion and energy expenditure during the first postnatal weeks in preterm babies, though not in the ones I described in my presentation. Within quite a wide range of catecholamine excretion there was no change in energy expenditure, though the type of substrate oxidized altered. Babies who excreted more epinephrine oxidized more lipids.

Dr. Jéquier: We have compared the thermogenic effect of dobutamine and dopamine and have shown quite clearly that the cardiovascular effect of increased peripheral resistance comes before the thermogenic effect. A considerable increase in dose is required before the thermogenic effect appears.

Dr. Koldovský: There is some controversy about the value of measuring the skinfold thickness. Did you take the reading immediately or did you use the 3-second or 6-second relaxation period?

Dr. Micheli: We designed skinfold calipers that closely mimic what the clinician does when measuring skinfold thickness. As clinicians we have in our hands or minds a certain amount of pressure to be applied by the caliper when we are taking a measurement. Our caliper gives
an electronic readout that mimics this action. It is not a dynamic measurement, which can be very variable in preterm infants.

REFERENCES


