

# Adiposity in small for gestational age preterm infants assessed at term equivalent age

M L Gianni, P Roggero, F Taroni, N Liotto, P Piemontese, F Mosca

Dipartimento di Scienze Materno-Infantili, Fondazione IRCCS "Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena", Università degli Studi di Milano, Milan, Italy

Correspondence to: Maria Lorella Gianni, Neonatal Intensive Care Unit, Fondazione IRCCS "Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena", University of Milan, Via Commenda 12, 20122 Milan, Italy; maria.gianni@unimi.it

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## ABSTRACT

**Objective:** Infants classified as small for gestational age are considered to have developed under adverse intrauterine conditions that lead to lack of fat mass accretion. The aim of this study was to test the null hypothesis that the fat mass in preterm small for gestational age infants assessed at term equivalent age was not different from that of full-term small for gestational age newborns.

**Design:** Observational study.

**Setting:** Northern Italy.

**Patients:** 67 small for gestational age preterm infants and 132 small for gestational age full-term newborns.

**Main outcome measures:** Growth and body composition, assessed by means of a paediatric air displacement plethysmography system, were measured at term equivalent age in the preterm infants and on the third day of life in the full-term newborns.

**Results:** The mean (SD) gestational age of preterm infants was 30.6 (2.3) weeks and their mean (SD) birth weight was 1140 (237) g. At assessment weight was not different between the preterm and full-term infants, whereas the percentage of total body fat mass was higher in the preterm infants (14.3% (SD 4.7%) vs 5.8% (SD 3.5%),  $p < 0.005$ ).

**Conclusions:** Preterm infants, born small for gestational age, appear to be at risk for increased adiposity, which is a risk factor for the development of the metabolic syndrome.

Infants classified as small for gestational age (SGA; birth weight <10th percentile) are considered to have developed under adverse intrauterine conditions that lead to lack of fat mass accretion. SGA infants have been reported to be shorter and thinner and to have a lower percentage of fat mass when compared to infants born appropriate for gestational age (AGA; birth weight between the 10th and 90th percentiles).<sup>1</sup> Lapillonne *et al*<sup>2</sup> found that the fat mass, lean mass and bone mineral content in SGA newborns were lower than in AGA infants of the same gestational age.

Several studies demonstrated that being SGA is associated with a higher risk of developing abnormal body composition<sup>3-5</sup> and long-term consequences including hypertension, increased cardiovascular mortality, and type 2 diabetes mellitus.<sup>6,7</sup>

Data on the body composition of preterm SGA infants evaluated at term equivalent age are scarce. Yau<sup>8</sup> demonstrated that the fat mass in preterm SGA infants assessed at term equivalent age was higher than in term AGA infants.

The aim of the present study was to test the null hypothesis that the fat mass in preterm SGA

## What is already known on this topic

- ▶ Infants classified as small for gestational age develop under adverse intrauterine conditions that lead to lack of fat mass accretion.
- ▶ The American Academy of Pediatrics recommends that preterm infants' growth duplicates fetal growth rates and that body composition replicates in utero body composition.

## What this study adds

- ▶ Preterm infants born small for gestational age appear to be at risk for increased adiposity, a risk factor for the metabolic syndrome in adulthood.
- ▶ Monitoring the quality of weight gain is important for determining optimal extrauterine growth and body composition of the small for gestational age preterm infant.

infants assessed at term equivalent age was not different from that of full-term SGA newborns.

## METHODS

### Patients

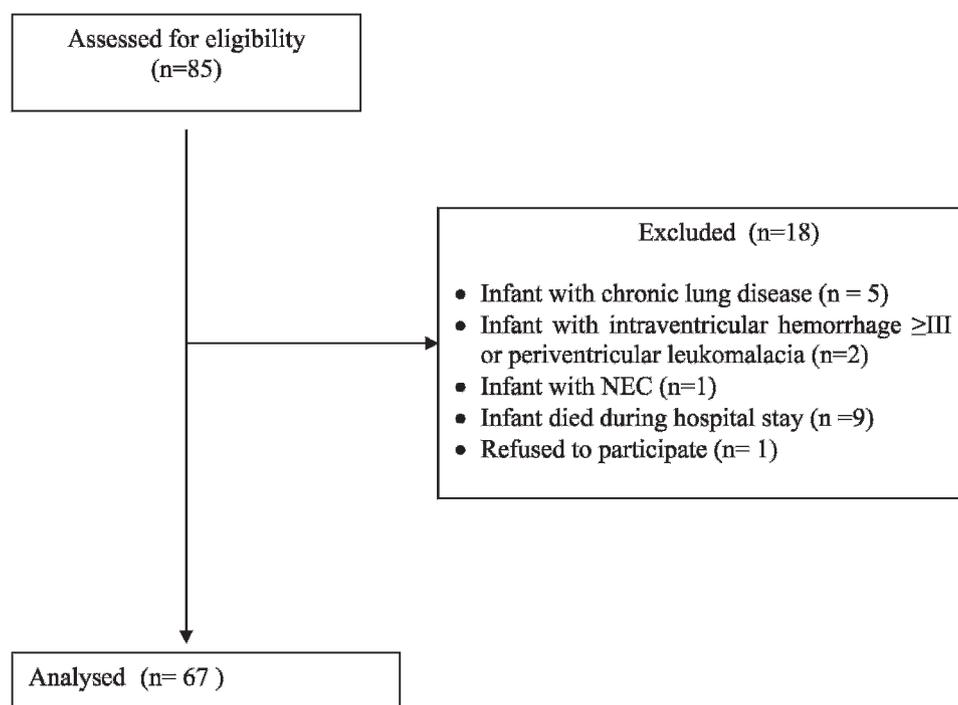
Infants were enrolled at birth. Eighty five preterm infants among all consecutive newborns admitted to the same institution from January 2007 to June 2008 were enrolled in the study. Figure 1 shows the CONSORT flow chart for the study.

Inclusion criteria were birth weight <10th percentile for gestational age according to Fenton's chart,<sup>9</sup> singleton pregnancy, gestational age  $\leq 34$  weeks and Caucasian race.

Exclusion criteria were the presence of congenital diseases, chromosomal abnormalities, severe cardiac, renal, endocrine or gastrointestinal diseases (ie, stage 3 necrotising enterocolitis according to the classification of Bell *et al*<sup>10</sup>), chronic lung disease, intraventricular haemorrhage grade III or higher, and periventricular leukomalacia.

A total of 132 full-term singleton newborns with a weight below the 10th percentile according to Tanner percentiles<sup>11</sup> and an obstetric history negative for maternal and/or fetal diseases were recruited as a reference group from an ongoing study on body composition in full-term newborns.

**Figure 1** CONSORT flow chart of the study. NEC, necrotising enterocolitis.



### Study design

A prospective, longitudinal, observational study was conducted. Basic subject characteristics (gestational age, gender) and anthropometric variables (weight, length and head circumference) at birth and at term equivalent age were recorded prospectively. Gestational age was based on the last menstrual period and first trimester ultrasonogram. Equivalent age was calculated using the chronologic age and adjusting for gestational age, that is, for the number of additional weeks from term (40 weeks).

The babies weight was measured on an electronic scale accurate to  $\pm 5$  g and body length was measured to the nearest 1 mm on a Harpenden neonatometer (Holtain, Crymych, Pembrokeshire, UK). Head circumference was measured to the nearest 1 mm using non-stretch measuring tape. All measurements were performed by trained nurses. Growth z scores were then calculated using EuroGrowth 2000 software (EuroGrowth Study Group, Vienna, Austria).

Body composition was assessed using an air displacement plethysmography system (PEA POD - Infant Body Composition System, LMI, Concord, CA). A detailed description of the PEA POD's physical design, operating principles, validation and measurement procedures is provided elsewhere.<sup>12–16</sup>

Briefly, the PEA POD assesses fat mass and fat free mass by direct measurements of body mass and volume and the application of a classic densitometric model where percentage of body fat is calculated using body density and pre-determined fat and fat free mass density values. Body fat was defined as body weight minus fat free mass. A constant fat mass density value of 0.9007 g/ml<sup>17, 18</sup> is used. Fat free mass density values are calculated as the sum of the contributions of the various components in the fat free mass compartment. Age and sex-specific fat free mass density values extrapolated from data reported in previous multi-compartment model studies are used.<sup>19, 20</sup>

In addition, the PEA POD uses data reported on the nature of total body water changes during the initial days of life in full term infants<sup>21</sup> and in preterm infants<sup>22–27</sup> to adjust the

contribution of the total body water component to fat free mass density values during the same period.

Infants were assessed nude in the PEA POD. Body mass was measured by the PEA POD's integrated electronic scale. Body volume was measured in the PEA POD's test chamber by applying gas laws that relate pressure changes to volume of air in the enclosed chamber. Each test lasted approximately 5 min, with the mass and volume measurements lasting 5–20 s and 2 min, respectively. The inter-observer coefficient of variation for the percentage of fat mass estimates was 0.3%.

Preterm infants received parenteral and minimal enteral feeding, with expressed breast milk or preterm formula, for a minimum of 2 weeks. Subsequently, up to discharge, the nutritional regimen was either fortified breast milk (2.2 g/100 ml and 82 kcal/100 ml) or preterm formula (2.4 g/100 ml and 80 kcal/100 ml) when breast milk was unavailable or insufficient. The fortifier used was supplemented with vitamin D and calcium. The mean daily energy and protein intakes (expressed as kcal/kg body weight/day and g/kg body weight/day, respectively) provided by parenteral and enteral nutrition during the hospital stay were collected from the medical records. At discharge parents were instructed to record in a diary the daily quantities of milk (expressed breast milk and/or preterm formula) consumed by the infants. The average daily energy and protein intakes from hospital discharge up to term equivalent age were then calculated. The energy and protein contents of breast milk were assumed to be 64 kcal/100 ml and 1 g/100 ml, respectively.

Full-term newborns were exclusively breast fed or, when breast milk was unavailable or insufficient, received a standard formula (1.4 g/100 ml and 67 kcal/100 ml).

Informed consent was obtained from the infants' parents and the study design was approved by the departmental Ethics Committee.

### Statistical analysis

Descriptive data are expressed as mean (SD) or number of observations (percentage). Comparisons between the preterm

and the full-term infants were assessed by the  $\chi^2$  test for discrete variables and Student's *t* test or the Mann-Whitney test for continuous variables. Linear regression analyses were performed to examine the effects of gestational age and birth weight, with gender as covariate, on the percentage of fat mass of the preterm infants assessed at term equivalent age. For each of the two independent variables (gestational age and birth weight), two separate regression models were developed, one using only gestational age and the other using only birth weight expressed in grams. This avoided possible collinearity between these two independent variables.

Statistical significance was set at the 0.05 level. All statistical analyses were performed using SPSS v 8 (SPSS, Chicago, IL).

## RESULTS

Anthropometric and body composition variables were available for 67 infants born preterm.

The basic characteristics of the infants born preterm were as follows: birth weight 1140 (237) g, length 36.7 (3.1) cm and head circumference 27 (2.0) cm. Mean gestational age was 30.6 (2.3) weeks. The mean gestational age of the full-term newborns was 39 (1.1) weeks and their mean birth weight was 2430 (148) g. The percentage of males was not significantly different between the preterm and the full-term infants (53% vs 50%, respectively;  $p = 0.06$ ). Table 1 shows the anthropometric and body composition variables in the preterm and the full-term infants at assessment.

Weight did not differ between the preterm and the full-term infants, but length and head circumference were smaller in the preterm infants compared with the full-term newborns. The preterm infants had a higher fat mass content than the full-term newborns. No gender related differences were found in the fat mass of either the preterm or the full-term newborns.

The mean duration of hospital stay was 60.6 (30) days in the preterm infants and 4 (0.5) days in the full-term infants.

The mean protein and energy intakes of the preterm infants were 2.69 (0.31) g/kg/day and 94 (10.5) kcal/kg/day, respectively. No significant association was found between the protein and energy intakes of the preterm infants and the fat mass assessed at term equivalent age. The mean duration of parenteral nutrition of the preterm infants was 20.8 (13.7) days. Expressed breast milk provided more than 50% of the daily energy and protein intakes in 45% ( $n = 30$ ) of the preterm infants and in 41% ( $n = 54$ ) of the full-term newborns.

Following linear regression analysis gestational age was negatively associated with the percentage of total body fat

mass of the preterm infants assessed at term equivalent age ( $R^2 = 0.14$ , unstandardised  $\beta$  coefficient =  $-0.73$ ;  $p = 0.005$ ), whereas gender and birth weight did not affect the dependent variable (fig 2).

## DISCUSSION

In this study the SGA infants born preterm, assessed at term equivalent age, had a higher fat mass content compared with the SGA full-term newborns, whereas weight did not differ between the two groups of infants. Furthermore, in the preterm infants the fat mass content at term equivalent age was negatively associated with gestational age. To our knowledge the present study is the first report in the literature comparing body composition between SGA preterm infants evaluated at term equivalent age and SGA full-term newborns.

Data on the body composition of preterm SGA infants evaluated at term equivalent age are scarce. Yau<sup>8</sup> found that the fat mass in 38 preterm SGA infants, assessed at term equivalent age by means of skin fold thickness, was higher than in term AGA infants. The authors speculated that differences between placental and postnatal nutrition, in addition to different energy utilisation, could account for these results.

The "thrifty phenotype" hypothesis, proposed by Hales and Barker,<sup>28</sup> suggests that the fetus adapts to an unfavourable prenatal environment by maintaining a constant nutrient supply to essential organs. As a possible consequence, SGA newborns at birth have significantly less adipose tissue compared with AGA infants.<sup>29</sup> Verkauskiene *et al*<sup>1</sup> have reported a significantly reduced percentage of fat mass, assessed by means of dual x ray absorptometry (DXA), in 89 full-term SGA infants (mean birth weight: 2480 g) when compared with infants born AGA. Lapillonne *et al*<sup>2</sup> found that fat mass, lean mass and bone mineral content in 20 SGA newborns were lower as compared to AGA infants of the same gestational age. However, fat mass was not different or was even increased in SGA newborns compared to AGA infants of similar weight and, accordingly, a lower gestational age. The authors suggested that these findings could be partially explained by the persistence of the proliferation of adipocytes during pregnancy even in the presence of intrauterine growth retardation.

In addition to poor nutrition during pregnancy, the majority of infants born preterm develop postnatal growth failure mainly because of a cumulative nutrient deficit which occurs during the first weeks of life.<sup>30</sup> Our results provide evidence that SGA infants born preterm develop not only postnatal growth retardation but also increased adiposity.

The finding of a negative correlation between gestational age and total fat mass content at term equivalent age further underlines the fact that the more immature a preterm infant is, the higher is the risk of developing increased adiposity. This could be because the extremely preterm infant, even in the absence of major clinical problems, is exposed for a longer length of time to an adverse extrauterine environment (ie, the neonatal intensive care unit). The American Academy of Pediatrics<sup>31</sup> recommends that normal intrauterine growth rate and body composition should be the primary goal when feeding preterm infants. Indeed growth is the result of a complex interaction among several factors, such as genetic background, nutrition and the environment. The two conditions – fetus and preterm infant – are very different as far as the environment and nutritional supply are concerned. The fetus receives a continuous supply of nutrients through the umbilical cord, while the preterm infant receives parenteral nutrition and/or is intermittently given milk or formula through the immature gut. The

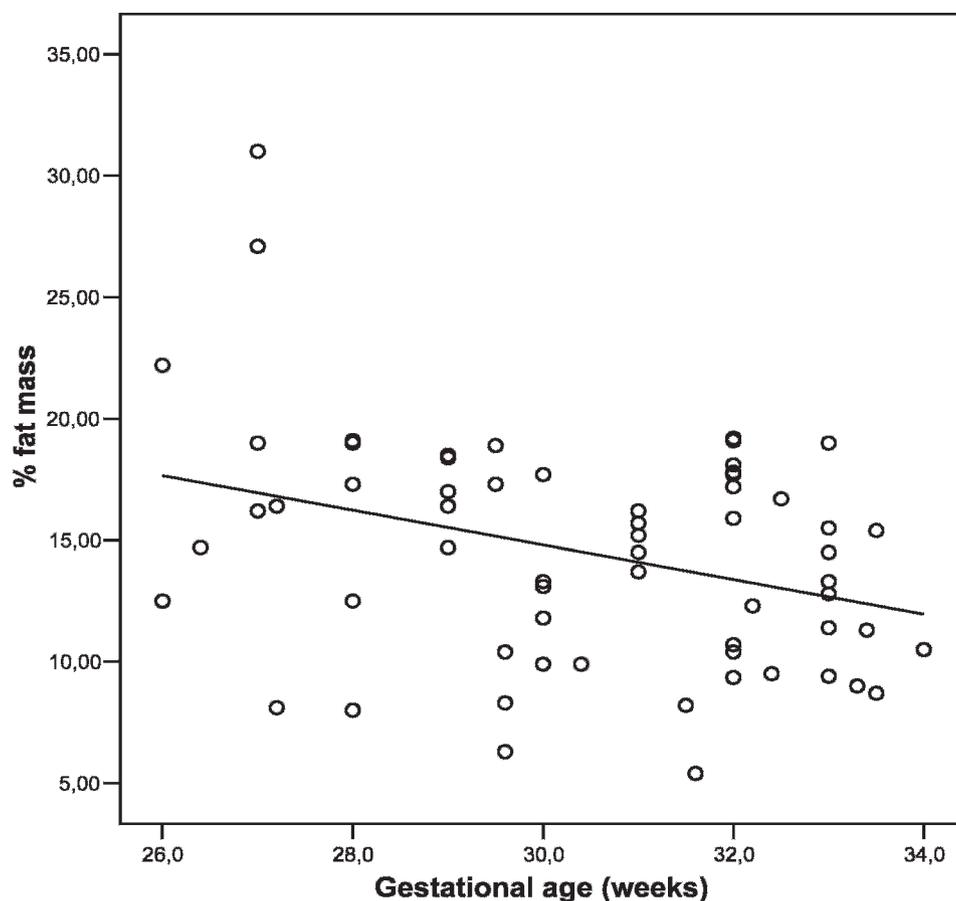
**Table 1** Anthropometric and body composition variables in the preterm and the full-term infants at assessment

	Preterm infants (n = 67)	Full-term newborns (n = 132)
Age at assessment (weeks)	39.4 (1.2)	39 (1.4)
Weight (g)	2402.9 (426)	2314 (213)
Weight z scores	-2.28 (0.9)	-2.5 (0.45)
Length (cm)	45.3 (2.25)*	48.1 (0.7)
Length z scores	-2.39 (1.1)*	-0.94 (0.4)
Head circumference (cm)	33.4 (1.1)*	34.3 (0.5)
Head circumference z scores	-0.81 (0.6)**	-0.12 (0.2)
Fat mass (g)	352.8 (157.7)*	138.8 (88.5)
Fat mass (%)	14.3 (4.7)*	5.8 (3.5)
Fat free mass (g)	2050 (290)	2180 (215.3)

Values are mean (SD).

\* $p < 0.005$  significantly different from full-term newborns; \*\* $p < 0.05$  significantly different from full-term newborns.

**Figure 2** Correlation between gestational age and fat mass assessed at term equivalent age in the preterm infants.



energy metabolism of the fetus is mainly dependent on carbohydrates, delivered at a rate that reflects energy use, rather than lipids. Indeed, the uptake of lipid by the fetus during the first trimester of pregnancy is low and gradually increases towards term, whereas after delivery fat becomes the primary supplier of energy. In addition, protein administration in the first days after delivery in preterm neonates is often limited because of concerns about lack of tolerance in these vulnerable infants, especially if born SGA, and so growth cannot occur.<sup>32</sup> It has been demonstrated that accretion of adipose tissue is directly correlated to energy intake and that an imbalance in the protein:energy ratio can lead to major deposition of fat mass rather than lean mass.<sup>33–36</sup> Van Goudoever *et al*<sup>34</sup> and Kashyap *et al*<sup>35–36</sup> have reported that fat deposition at the recommended intake of 120–130 kcal/kg/day is higher than in the reference fetus.

The various differences between fetal and postnatal nutrition could partially explain the findings of the present study, although nutrition is estimated to be responsible for only half of the variance in the growth pattern of the early postnatal period.<sup>37</sup> Theoretically, whereas the SGA full-term newborns have completed their growth after being continuously exposed to an adverse intrauterine environment, the SGA infants born preterm could benefit from the change to an extrauterine environment. However, the preterm infants born SGA fail to maintain the same relationship between protein synthesis and fat deposition compared to the fetus, probably because of relative postnatal malnutrition. On the other hand, the increased adiposity could represent an adaptive response to postnatal life, for example to increase energy stores or improve thermoregulation.<sup>38</sup>

It is being increasingly recognised that being born SGA is associated with a high risk of developing increased and aberrant adiposity and metabolic diseases later in life, particularly hypertension, increased cardiovascular mortality, and type 2 diabetes mellitus. This association was investigated longitudinally in children aged 2, 3, and 4 years by Ibáñez *et al*<sup>39</sup> who found greater adiposity and insulin resistance in 29 SGA infants as compared to AGA infants by the age of 4 years. We have previously demonstrated that in children born preterm, assessed at school age by means of DXA, being SGA positively affected the trunk fat mass content.<sup>5</sup> Labayen *et al*<sup>3</sup> demonstrated an inverse association between birth weight and central adiposity in adolescents born SGA. Meas *et al*<sup>40</sup> reported a greater fat mass with more abdominal fat in adults born SGA evaluated at 22 and 30 years of age.

It appears that the occurrence of unfavourable events during a critical period (pregnancy and early infancy) plays a major role in determining the extent of later adverse consequences for adult health.

Based on the present findings, it is clear that accurate and non-invasive assessment of the quality, in addition to the amount, of weight gain in these vulnerable infants is required. Such assessments allow better understanding of the relationship between birth weight or time in utero and future development and, more importantly, allow us to better individualise and optimise nutritional management in these vulnerable infants.

**Competing interests:** None.

**Ethics approval:** The study design was approved by the departmental Ethics Committee.

**Patient consent:** Parental consent obtained.

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