CLINICAL STUDY

Impact of fetal growth restriction on body composition and hormonal status at birth in infants of small and appropriate weight for gestational age

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Abstract

Background: Fetal growth restriction (FGR) has been related to several health risks, which have been generally identified in small-for-gestational age (SGA) individuals.

Objective: To evaluate the impact of FGR on body composition and hormonal status in infants born either small- or appropriate-for-gestational age (AGA).

Methods: Fetal growth was assessed by ultrasound every 4 weeks from mid-gestation to birth in 248 high-risk pregnancies for SGA. Fetal growth velocity was calculated as change in the estimated fetal weight percentiles and FGR defined as its reduction by more than 20 percentiles from 22 gestational weeks to birth. Impact of FGR on body composition, cord insulin, IGF-I, IGF binding protein-3 (IGFBP-3), and cortisol concentrations was assessed in SGA and AGA newborns.

Results: Growth-retarded AGA infants showed significantly reduced birth weight, ponderal index, percentage of fat mass, and bone mineral density when compared with AGA newborns with stable intrauterine growth. Cord IGF-I and IGFBP-3 concentrations were significantly decreased in growth-retarded infants in both SGA and AGA groups. Cord insulin concentration was significantly lower and cord cortisol significantly higher in AGA infants with FGR versus AGA newborns with stable intrauterine growth. After adjustment for gestational age and gender, birth weight was directly related to fetal growth velocity and cord IGF-I concentration. The variation in infant’s adiposity was best explained by fetal growth velocity and cord insulin concentration.

Conclusions: FGR affects body composition and hormonal parameters in newborns with birth weight within the normal range, suggesting these individuals could be at similar metabolic risks as SGA.

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Introduction

A number of short- and long-term health risks for subjects born small-for-gestational age (SGA) have been identified. It is well recognized that fetuses at the extremes of normal birth weight range are at an increased risk of perinatal morbidity, mortality, and adverse developmental outcomes (1, 2). The long-term consequences of small size at birth have also been reported by numerous studies, including hypertension (3), increased cardiovascular mortality (4), insulin resistance, impaired glucose tolerance, and type 2 diabetes mellitus (5, 6). Recent research has suggested that programming of the endocrine axis and the cardiovascular system occurs during fetal development and may be affected by intrauterine growth retardation (IUGR) (7). A vast majority of these studies referred to individuals born SGA, a term that refers to size at birth but not to intrauterine growth pattern. However, not all SGA babies will suffer from IUGR and not all growth-retarded fetuses will be born SGA (8). Birth weight is a final result of fetal growth in utero, and IUGR or fetal growth restriction (FGR) are terms that indicate fetal growth pattern with reduced fetal growth velocity, presuming that at least two assessments of fetal size at different time points are available. Separating small babies, who are small simply as a result of adaptation to maternal size, from those who have suffered FGR presents a diagnostic challenge, because it is the FGR group which is at an increased perinatal risk and needs to be identified clinically (2).

In addition to gestational age and gender, other pregnancy characteristics, such as maternal height and weight before pregnancy, parity, and ethnicity, account for a considerable part of the variation in fetal growth velocity and weight at birth (9). A computer
program, named customized birth weight standards, has been created by Gardosi et al. in which estimated fetal weight (EFW) centiles are adjusted for all these variables (10).

Apart from physiological variables, the regulation of fetal growth depends mainly on the nutrient availability to the fetus, the predominant axis being glucose–insulin–insulin-like growth factor-I (IGF-I) (11). Numerous studies have shown SGA newborns having significantly lower levels of IGF-I, IGF binding protein-3 (IGFBP-3), and insulin than appropriate-for-gestational age (AGA) newborns (12, 13). However, few studies have addressed the problem of inadequate intrauterine growth of infants with appropriate for gestational age birth weight, who failed to reach their genetic potential (14, 15). Therefore, the objective of the present study was to evaluate the impact of fetal growth pattern assessed by the customized method on body composition and hormonal status in both low and normal birth weight newborns.

Materials and methods

A total of 248 pregnant women were recruited between November 2003 and September 2005 at their first or second trimester visit in the Maternity units of Hôpital Robert Debré in Paris (n = 193) and Hôpital Edouard Herriot in Lyon (n = 55). The study population consisted of women of Caucasian origin considered at risk of SGA and were selected on the following criteria: pre-existing hypertension, smoking more than five cigarettes per day, a history of SGA in previous pregnancies or among both parents, a history of pregnancy-induced hypertensive disorder, maternal height < 152 cm (corresponding to −2 SD in height for French women), uterine malformations, abnormal uterine or umbilical arteries Doppler or small fetal size at second-trimester ultrasound examination.

All women had an ultrasound pregnancy date evaluation at 12 gestational weeks, which has been a routine procedure in France since 1974.

The study protocol was reviewed and approved by the ethical committee of the University of Paris, St Louis and all parents gave written informed consent.

Assessment of fetal growth

Fetal growth was assessed every 4 weeks by ultrasound from 22 to 36 weeks of gestation. All four ultrasound scans were performed by the same observer for each woman under a standardized protocol according to the guidelines of College des Echographistes de France. Fetal weight was estimated using second Hadlock formula, which includes abdominal circumference (AC), biparietal diameter (BPD), and femur length (FL) measurements

\[
\text{Log}_{10} \text{fetal weight (g)} = 1.335 - 0.0034 \times AC \times FL + 0.0316 \times BPD + 0.0457 \times AC + 0.1623 \times FL
\]

(16). For analysis of fetal growth pattern, the customized fetal and birth weight percentiles were calculated for each case with a computer program, which adjusts for parity, infant’s gender, maternal weight, height, and ethnic group (17). This program contains coefficients for these physiological variables based on 40,000 ultrasound dated pregnancies in Nottingham and was described in detail elsewhere (9). Intrauterine growth velocity was calculated as the change in EFW percentiles from 22 gestational weeks (GW) until birth. FGR was defined as a reduction in EFW by more than 20 percentiles over this period (15). At birth, SGA was defined as birth weight below the 10th customized percentile and AGA as above the 10th customized percentile (9).

Using the methods described, all 248 infants were classified into four groups: SGA-FGR (n = 45), SGA with normal fetal growth velocity (SGA-N, n = 44), AGA-FGR (n = 60), and AGA with normal fetal growth velocity (AGA-N, n = 99; Fig. 1). All infants were born from singleton pregnancies after 33–42 weeks of gestation and had no obvious malformations.

Neonatal anthropometry and body composition assessment

Birth weight was recorded within 10 g by midwives using an electronic scale. The study children were measured by trained medical personnel. 72 h after birth. The birth length was measured on a standard infant measuring board and recorded to the nearest millimeter. Body composition at postnatal day 3 (fat mass, lean mass, and bone mineral density) was assessed by dual X-ray absorptiometry (DEXA) scan (LunaR Prodigy DXP, GE Medical Systems, Madison, WI, USA), with a specific program for small body weight, using a specific ‘phantom’ for calibration (18, 19).

Hormonal analysis

Mixed venous and arterial umbilical cord blood samples were collected from 183 infants born to mothers following the study protocol: 31 SGA-FGR, 28 SGA-N, 43 AGA-FGR, and 81 AGA-N newborns. Totally, 139 infants were born at Robert Debré Hospital in Paris and 44 were born at Eduard Heriot Hospital in Lyon. Infants for whom blood samples were available did not differ from the rest of the cohort in terms of gestational age, birth anthropometry, and body composition parameters. The cord blood samples obtained were centrifuged and serum was separated and stored at −80 °C until analysis.

Serum IGF-I was measured using an IRMA kit (IGF-I-RIACT) from Cis Bio International (Gif-sur-Yvette, France) and serum IGFBP-3 using an IRMA kit (ACTIVE IGFBP-3 IRMA) from DSL (Cergy Pontoise, France).

Serum insulin was measured using an IRMA kit (BI-INS-IRMA) from Cis Bio International. The cross-reactivity
with proinsulin and derived metabolites was < 1%. The assay sensitivity was 0.5 mIU/l.

Serum cortisol was measured by an automated competitive chemiluminescent immunoassay (ACS 180; Bayer Diagnostics).

Statistical analysis

Infants’ anthropometric and body composition parameters at birth are given as mean ± S.D.

Umbilical cord IGF-I, IGFBP-3, insulin and cortisol concentrations were log-transformed before analysis to normalize distribution. Comparisons of anthropometric, body composition, and hormonal parameters among the four groups of newborns were made using general linear model with adjustment for gestational age and gender. For this purpose, general factorial models with Bonferroni confidence interval adjustment were used, with anthropometric, body composition, and hormonal parameters as dependent variables, infants’ group as a fixed factor, and gestational age and gender as the covariates in each model.

The relationship between continuous variables was assessed by partial correlation analysis with adjustment for gestational age and gender.

The relative influence of determinants of infants’ birth weight and adiposity was assessed using multiple stepwise regression models on the whole cohort.

All analyses were performed using the SPSS program (for Windows, version 10).

Results

Neonatal anthropometry and body composition

In these high-risk pregnancies, 89 infants (36%) at birth were classified as SGA. SGA newborns had somewhat shorter gestational age and higher frequency of female gender than AGA infants (Table 1). Therefore, further comparisons of anthropometric and body composition parameters between the groups were performed with adjustment for gestational age and gender. As expected, SGA infants were considerably lighter, shorter, and thinner, and had smaller mean HC, lower lean mass, percent of fat mass, and bone mineral density when compared with infants born AGA (Table 1).

Using the criterion of reduction in EFW by 20 or more percentiles from mid-gestation to birth, the FGR was found in 51% of SGA and in 38% of AGA infants of our study population. The comparisons of anthropometric characteristics and body composition between infants with and without FGR, adjusted for gestational age and gender, are given in Table 2. Anthropometric measurements and body composition parameters at birth were lower in the SGA-FGR when compared with the SGA-N group, but the differences were not statistically significant, except for bone mineral density which was significantly lower in the SGA-FGR group (Table 2). In contrast, FGR had a significant influence on the anthropometric measurements and body composition in the group of AGA infants: AGA-FGR infants were significantly lighter, shorter, and thinner, and they had significantly less of lean and fat mass and lower BMD than AGA infants with stable intrauterine growth velocity (Table 2).

Hormonal status at birth

When looking at the hormonal status at birth after correction for gestational age and gender, it was found that IGF-I and IGFBP-3 concentrations were lower in the cord blood of infants with FGR in both SGA and AGA groups (Fig. 2A and B). The umbilical cord insulin concentration was significantly decreased in the AGA-FGR versus AGA-N group. The cord insulin concentration was also lower in the SGA-FGR versus SGA-N group, but the difference failed to reach statistical
Table 1 Anthropometry and body composition at birth in infants born either small-for-gestational age (SGA) or appropriate-for-gestational age (AGA).

<table>
<thead>
<tr>
<th></th>
<th>SGA</th>
<th>AGA</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=89)</td>
<td>(n=159)</td>
<td></td>
</tr>
<tr>
<td>Gestational age (days)</td>
<td>270±14</td>
<td>274±11</td>
<td>0.004</td>
</tr>
<tr>
<td>M/F ratio</td>
<td>33/56</td>
<td>82/77</td>
<td>0.05</td>
</tr>
<tr>
<td>% Born by caesarean section</td>
<td>27.1</td>
<td>17.8</td>
<td>0.14</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>2480±464</td>
<td>3227±449</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Birth weight (percentiles)</td>
<td>3.7±2.9</td>
<td>41.3±24.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Birth length (cm)</td>
<td>46.5±2.3</td>
<td>49.2±2.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ponderal index (g/cm³)</td>
<td>2.55±0.2</td>
<td>2.77±0.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>32.9±1.4</td>
<td>34.2±1.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lean mass (g)</td>
<td>2222±269</td>
<td>2646±364</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fat mass (g)</td>
<td>434±306</td>
<td>653±304</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fat mass (%)</td>
<td>15.6±5.9</td>
<td>19.2±6.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Bone mineral density (g/cm²)</td>
<td>0.316±0.09</td>
<td>0.340±0.07</td>
<td>0.056</td>
</tr>
</tbody>
</table>

*P values between the groups are shown after adjustment for gestational age and gender, where appropriate.

The determinants of infants’ birth weight and parameters of body composition were analyzed in multiple linear regression models. The variation in birth weight was best explained by the variation in gestational age, intrauterine growth velocity, and cord IGF-I concentrations, having a positive effect on birth weight; female gender was inversely associated with birth weight (Table 3). The same variables were significantly associated with infants’ lean mass assessed by DEXA (gestational age: r=0.55, P<0.0001; intrauterine growth velocity: r=0.32, P=0.001; female gender: r=-0.24, P<0.0001; log cord IGF-I: r=0.22, P=0.003). Infants’ adiposity at birth, expressed in percentage of fat mass, was significantly and positively associated with intrauterine growth velocity, female gender, and cord insulin concentration (Table 4). Of all these determinants entered in the multivariate model, only the intrauterine growth velocity was significantly associated with infants’ lean mass and parameters of body composition.
related to the bone mineral density of newborns ($r=0.45$, $P<0.0001$).

**Discussion**

This paper reports the impact of FGR on birth weight, body composition, and hormonal status in infants born of small and appropriate for gestational age birth weight. Even if it is generally recognized that fetal growth retardation confers an increased risk for perinatal morbidity and mortality, the definition of FGR still remains problematic. An adequate estimation of fetal growth requires appropriate standards that take individual variation into account. A recently created computer program provides a method to predict fetal weight gain across the gestation, adjusting for individual physiological variables, such as fetal gender, gestational age, parity, maternal height, weight in early pregnancy, and ethnic group (9). Such customized fetal growth estimation allows to reduce false-positive diagnosis of FGR in low-risk population (20) and significantly improves identification of infants who have failed to reach their genetic potential and who are at increased risk for adverse perinatal events in geographically different high-risk populations (21, 22).

Therefore, when assessing fetal growth in this study, EFWs during four ultrasound scans from mid-gestation to near-term and infants’ birth weights were converted into individually adjusted percentiles using a customized growth standard method (17). The intrauterine growth velocity, calculated from these five time points, have been found to be one of the best determinants of birth weight and all body composition parameters, even after adjustment for gestational age and gender.

Using the criterion of reduction in EFW by 20 or more percentiles from mid-gestation to birth, the FGR was found in 51% of SGA infants and in 38% of AGA infants. This strikingly high proportion of FGR, especially among newborns of normal birth weight, is most likely due to the study population selection from high-risk pregnancies. Importantly, all anthropometric and body composition parameters were significantly reduced in AGA infants with restricted fetal growth as compared with AGA infants with stable intrauterine growth, indicating a reliability of the method used for the definition of FGR. However, the two groups of SGA infants were surprisingly similar in all these parameters, except for bone mineral density, which was significantly lower in growth-retarded SGA infants when compared with SGA newborns with normal fetal growth velocity. One of the possible explanations could be the presence of early FGR in some SGA infants classified as having stable intrauterine growth velocity that could not be detected on ultrasound examinations started by mid-gestation. Indeed, at 22 gestational weeks, the EFW was already below the 10th percentile in 45% of SGA-N infants in contrast to only in 4% of growth-retarded

*Figure 2* Cord concentration of IGF-I, IGFBP-3, insulin, and cortisol in SGA and AGA infants with and without fetal growth restriction. *P values between SGA-FGR/SGA-N and AGA-FGR/AGA-N groups are shown after adjustment for gestational age and gender.

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Table 3 Determinants of the variation in birth weight by multiple linear regression analysis (stepwise). Variables entered: gestational age, gender, intrauterine growth slope, log cord insulin-like growth factor-I (IGF-I), log cord insulin, and log cord cortisol concentrations.

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Coefficient B</th>
<th>P</th>
<th>Adjusted r²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (days)</td>
<td>27</td>
<td>&lt;0.0001</td>
<td>0.391</td>
</tr>
<tr>
<td>Intrauterine growth velocity</td>
<td>470</td>
<td>&lt;0.0001</td>
<td>0.165</td>
</tr>
<tr>
<td>Log cord IGF-I</td>
<td>531</td>
<td>&lt;0.0001</td>
<td>0.042</td>
</tr>
<tr>
<td>Female gender</td>
<td>-130</td>
<td>0.016</td>
<td>0.018</td>
</tr>
<tr>
<td>Total model*</td>
<td>&lt;0.0001</td>
<td>0.616</td>
<td></td>
</tr>
</tbody>
</table>

*F value for the final model with all four predictors, 68.0.

SGA. Otherwise, it could be argued that the body composition of newborns is probably related to the body size per se. However, it is important to stress that the customized method used in this study to define fetal growth adjusts for all non-pathological variables; thus, all babies with birth weight below the 10th percentile could theoretically be considered as growth retarded, i.e. failing to reach their genetic potential, especially in this population of high-risk pregnancies.

In contrast to anthropometry and body composition, we found a significant impact of FGR on the concentration of growth factors at birth in both SGA and AGA groups. Significantly higher mean cord IGF-I and IGFBP-3 levels and the tendency to higher mean cord insulin concentration in ‘constitutional’ versus FGR groups would be in favor of a better nutritional status of ‘constitutional’ SGA and AGA infants, as fetal undernutrition lowers IGF-I levels (23). Previous studies have shown that both fetal and neonatal sizes correlate directly with circulating IGF-I levels, SGA babies having significantly lower levels of both IGF-I and IGFBP-3 than AGA newborns (12, 24). In the present study, we have evidenced that not only fetal and neonatal sizes, but also fetal growth pattern is strongly associated with circulating levels of growth factors over the spectrum of birth weights. A direct relationship of umbilical cord IGF-I concentration and newborns’ total bone mineral content has been reported in previous studies; however, this relationship was no longer significant after adjustment for neonatal bone size (25). It was therefore suggested that cord IGF-I is more closely related to the size of neonatal skeleton than to its degree of mineralization. In our study, neonatal bone mineral density had the strongest direct relationship with intrauterine growth velocity but not with cord IGF-I concentration.

There is now increasing evidence that the development of metabolic and cardiovascular diseases in adulthood is related to the adverse intrauterine environment (26). This association is continuous and represents birth weights even within the normal range, rather than severely undersized, multiple or premature babies (27). Thus far, the mechanism of such ‘fetal programming’ is not clear. One major hypothesis is the ‘thrifty phenotype’ concept which states that fetal undernutrition during a sensitive developmental period or window affects the development and organization of specific tissues leading to the development of their resistance to the action of insulin (26). The absorptiometry results in our study have shown that SGA and AGA infants with FGR have significantly reduced lean and fat mass at birth when compared with normally grown AGA infants. Previous ultrasound studies on fetal growth have shown that growth-retarded fetuses have a disproportionate reduction in fat mass when compared with lean mass (28, 29). It is well known that the majority of SGA or IUGR infants demonstrate a postnatal catch-up growth (30), which is a phenomenon compensatory to abnormal thinness or smallness at birth in order to bring each subject to his/her own ‘genetic’ centile. However, since there is little cell replication of muscle tissue (31) postnatally, catch-up growth promotes an excess of adiposity (6), a more central pattern of fat distribution (32, 33), and a lower lean body mass (34) in childhood and adulthood, constituting an increased risk of insulin resistance and metabolic disturbances in these subjects.

Another hypothesis of fetal ‘programming’ implicates fetal overexposure to glucocorticoids (35). In mammalian models and in humans, exposure to supraphysiological levels of glucocorticoids causes fetal growth retardation (36). Accordingly, we have found higher levels of cord cortisol in babies experiencing intrauterine growth restriction. Fetal glucocorticoid levels are normally much lower than those in maternal circulation. This gradient is thought to be maintained by placental enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) which catalyzes the rapid metabolism of active glucocorticoids to physiologically inert 11-ketoforms (37). The efficiency of placental 11β-HSD2 varies considerably and its lowest activity, and presumably the highest fetal exposure to maternal glucocorticoids, is seen in babies with smaller birth

Table 4 Determinants of the variation in infants’ adiposity at postnatal day 3 by multiple linear regression analysis. Variables entered: gestational age, gender, intrauterine growth slope, log cord insulin-like growth factor-I (IGF-I), log cord insulin, and log cord cortisol concentrations.

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Coefficient B</th>
<th>P</th>
<th>Adjusted r²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrauterine growth velocity</td>
<td>5.7</td>
<td>0.001</td>
<td>0.169</td>
</tr>
<tr>
<td>Female gender</td>
<td>3.7</td>
<td>0.001</td>
<td>0.106</td>
</tr>
<tr>
<td>Log cord insulin</td>
<td>4.8</td>
<td>0.01</td>
<td>0.046</td>
</tr>
<tr>
<td>Total model*</td>
<td>&lt;0.0001</td>
<td>0.321</td>
<td></td>
</tr>
</tbody>
</table>

*F value for the final model with all three predictors, 16.5.
weights (38). Importantly, maternal protein restriction in rodents reduces the activity of placental 11β-HSD2 (39), suggesting that environmental insults may operate through glucocorticoids in exerting their programming effects (40).

In summary, our data clearly demonstrate that FGR significantly affects body composition and hormonal status even in newborns of AGA birth weight. Further prospective follow-up studies are needed to clarify whether these subjects are equally exposed to the long-term metabolic outcomes as individuals born SGA.

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