Breast-feeding vs Formula-feeding for Infants Born Small-for-Gestational-Age: Divergent Effects on Fat Mass and on Circulating IGF-I and High-Molecular-Weight Adiponectin in Late Infancy

Francis de Zegher, Giorgia Sebastiani, Marta Diaz, María Dolores Gómez-Roig, Abel López-Bermejo, and Lourdes Ibáñez

Department of Reproduction, Development, and Regeneration (F.d.Z.), University of Leuven, 3000 Leuven, Belgium; Hospital Sant Joan de Déu (G.S., M.D., M.D.G.-R., L.I.), University of Barcelona, 08950 Esplugues, Barcelona, Spain; Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM) (G.S., M.D.), Instituto de Salud Carlos III, Madrid, Spain; and Department of Pediatrics (A.L.-B.), Dr Josep Trueta Hospital, 17007 Girona, and Girona Institute for Biomedical Research, 17007 Girona, Spain

Context: Fetal growth restraint, if followed by rapid weight gain, confers risk for adult disease including diabetes. How breast-feeding may lower such risk is poorly understood.

Objective, Study Participants, Intervention, Outcomes: In infants born small-for-gestational-age (SGA), we studied the effects of nutrition in early infancy (breast-feeding vs formula-feeding; BRF vs FOF) on weight partitioning and endocrine markers in late infancy. Body composition (by absorptiometry), fasting glycemia, insulin, IGF-I, and high-molecular-weight (HMW) adiponectin were assessed at 4 and 12 months in BRF controls born appropriate-for-GA (N = 31) and in SGA infants receiving BRF (N = 48) or FOF (N = 51), the latter being randomized to receive a standard formula (FOF1) or a protein-rich formula (FOF2).

Setting: The study was conducted in a University Hospital.

Results: SGA-BRF infants maintained a low fat mass and normal levels of IGF-I and HMW adiponectin. In contrast, SGA-FOF infants normalized their body composition by gaining more fat; this normalization was accompanied by a marked fall in HMW adiponectinemia and, in FOF2 infants, by elevated IGF-I levels. In late infancy, SGA-BRF infants were most sensitive to insulin, even more sensitive than appropriate-for-GA–BRF controls.

Conclusions: Because the health perspectives are better for SGA-BRF than for SGA-FOF infants, the present results suggest that FOF for SGA infants should aim at maintaining normal IGF-I and HMW-adiponectin levels rather than at normalizing body composition. Nutriceutical research for SGA infants may thus have to be redirected. **(*J Clin Endocrinol Metab* 98: 1242–1247, 2013)**

Infants born small-for-gestational-age (SGA) are at higher risk for adult diseases such as diabetes and hypertension (1). Long-term studies have shown that such metabolic and cardiovascular risk is modulated by nutrition in early infancy, breast-feeding (BRF) being followed by a relatively low risk, and protein-rich formula-feeding (FOF) by a relatively high risk (2, 3).

In 2005–2006 (thus before the risk conferred by protein-rich FOF was established), we designed a study aiming to disclose early divergences in the endocrine state and body composition of SGA infants receiving either BRF or FOF (standard or protein-rich formula) across early infancy (0–4 months). This study disclosed that catch-up growth of SGA infants in early infancy prioritizes the re-

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

Received September 28, 2012. Accepted December 10, 2012.
First Published Online January 30, 2013

Abbreviations: AGA, appropriate-for-gestational-age; BMC, bone mineral content; BRF, breast-feeding; CV, coefficient of variation; FOF, formula-feeding; HMW, high molecular weight; SGA, small-for-gestational-age.

covery of lean mass, and it identified circulating IGF-I and high-molecular-weight (HMW) adiponectin at age 4 months as early markers of divergence between SGA-BRF and SGA-FOF infants (4). Herein we report the longitudinal findings in late infancy (4–12 months).

Subjects and Methods

Study population

The study cohort consisted of 130 infants (Table 1) recruited (Supplemental Figure 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org) into a longitudinal study that assesses the body composition and endocrine-metabolic state of SGA infants, as compared to appropriate-for-gestational-age (AGA)-BRF controls, in the first years after birth (4–7). This follow-up study focused on length gain, weight partitioning, and fasting glycemia and circulating insulin, IGF-I, and HMW adiponectin between 4 and 12 months.

Specific inclusion criteria were as follows:

- Birth at Hospital Sant Joan de Déu, Barcelona, after an uncomplicated, term (37–42 weeks), singleton pregnancy (no maternal hypertension; no gestational diabetes; no alcohol abuse; no drug addiction);
- Birth weight between 2.9 and 3.9 kg for AGA and between 1.9 and 2.6 kg for SGA infants; cord serum available at enrollment (there were logistic restraints; step 1 in Supplemental Figure 1);
- Exclusive breastfeeding for 4 months in AGA controls; either exclusive breastfeeding for 4 months, or exclusive feeding with assigned formula in SGA infants (see below);
- At 4 and 12 months, auxological, body composition, and endocrine assessments (see below);
- Written, informed consent by at least one of the parents, in Spanish/Catalan language, at birth (as expected, the parental consent rate was higher for SGA than for AGA infants; step 2 in Supplemental Figure 1).

The exclusion criteria were complications at birth (need for resuscitation or parenteral nutrition) and congenital malformations.

The fraction of infants with complete follow-up between 4 and 12 months was higher in the SGA than in the AGA subpopulation (80% vs 30% of eligible infants; step 3 in Supplemental Figure 1). No differences were detected in the baseline features of infants who completed vs those who did not complete the follow-up.

Mothers of SGA infants were recommended to give BRF but many preferred nevertheless to give FOF (step 4 in Supplemental Figure 1). After birth, SGA-FOF infants were randomly assigned (1:1) to receive FOF1 (Enfalac 1; Mead Johnson, Madrid, Spain) or FOF2 (Enfalac for Prematures and Low-Birthweight Infants; Mead Johnson) (4). The milk concentration was 12.9% and the recommended volume was 150 mL/kg/d. FOF2 contains less fat and more protein than human milk; FOF1 has a composition

Table 1. Characteristics of Infants Born AGA or SGA and Receiving Exclusively BRF or FOF With Either FOF1 or FOF2 Across Early Infancy (0–4 mo)

	AGA-BRF	All SGA	SGA-BRF[a]	SGA-FOF1[a]	SGA-FOF2[a]	SGA-FOF
N (girls, n)	31 (14)	99 (53)	48 (26)	28 (16)	23 (11)	51 (27)
Primigravida (n, %)	21 (68)	67 (68)	36 (75)	20 (71)	11 (48)	31 (60)
Maternal smoking (n, %)	4 (13)	32 (32)	12 (25)	14 (50)	6 (26)	20 (39)
Cesarean section (n, %)	1 (3)	35 (35)	15 (31)	13 (46)	10 (43)	20 (39)
Gestational age (wk)	39.6 ± 0.2	38.5 ± 0.1[e]	38.7 ± 0.2[c]	38.5 ± 0.3[d]	38.1 ± 0.3[e]	38.3 ± 0.2[e]
At birth						
Birth weight (kg)	3.3 ± 0.04	2.3 ± 0.02[e]	2.3 ± 0.03[e]	2.3 ± 0.04[e]	2.3 ± 0.04[e]	2.3 ± 0.03[e]
Birth length (cm)	49.8 ± 0.2	45.8 ± 0.2[e]	46.0 ± 0.3[e]	45.7 ± 0.3[e]	45.4 ± 0.3[e]	45.6 ± 0.2[e]
Birth weight Z-score	0.0 ± 0.1	−2.2 ± 0.0[e]	−2.3 ± 0.1[e]	−2.3 ± 0.1[e]	−2.1 ± 0.1[e]	−2.2 ± 0.1[e]
Birth length Z-score	−0.1 ± 0.1	−1.7 ± 0.1[e]	−1.7 ± 0.1[e]	−1.8 ± 0.1[e]	−1.8 ± 0.1[e]	−1.8 ± 0.1[e]
Ponderal index (kg/m^3)	26.8 ± 0.3	24.0 ± 0.3[e]	24.0 ± 0.4[e]	23.8 ± 0.6[e]	24.3 ± 0.5[e]	24.0 ± 0.4[e]
At 4 mo						
Age (d)	126 ± 2	128 ± 1	130 ± 1[b]	127 ± 1	126 ± 2	126 ± 1
Weight (kg)	6.9 ± 0.1	5.9 ± 0.1[e]	5.9 ± 0.1[e]	5.9 ± 0.1[e]	5.9 ± 0.1[e]	5.9 ± 0.1[e]
Length (cm)	63.5 ± 0.4	60.4 ± 0.2[e]	60.3 ± 0.3[e]	60.2 ± 0.5[e]	60.9 ± 0.5[e]	60.5 ± 0.3[e]
Weight Z-score	0.3 ± 0.2	−0.9 ± 0.1[e]	−0.9 ± 0.1[e]	−0.9 ± 0.1[e]	−0.9 ± 0.1[e]	−0.9 ± 0.1[e]
Length Z-score	0.1 ± 0.2	−1.0 ± 0.1[e]	−1.0 ± 0.1[e]	−1.0 ± 0.1[e]	−0.8 ± 0.1[d]	−0.9 ± 0.1[e]
Ponderal index (kg/m^3)	27.1 ± 0.6	27.3 ± 0.4	27.7 ± 0.8	27.4 ± 0.5	26.6 ± 0.4	27.0 ± 0.3
At 12 mo						
Age (d)	385 ± 4	383 ± 2	384 ± 2	383 ± 3	382 ± 3	382 ± 2
Weight (kg)	10.1 ± 0.2	9.1 ± 0.1[e]	9.0 ± 0.1[e]	9.0 ± 0.2[e]	9.4 ± 0.2[b]	9.2 ± 0.1[e]
Length (cm)	74.4 ± 0.5	73.6 ± 0.3	73.5 ± 0.5	73.0 ± 0.4[b]	74.4 ± 0.7	73.6 ± 0.4
Weight Z-score	0.1 ± 0.2	−0.8 ± 0.1	−0.9 ± 0.1[e]	−0.9 ± 0.2[d]	−0.5 ± 0.2[b]	−0.7 ± 0.1[e]
Length Z-score	−0.3 ± 0.2	−0.8 ± 0.1[b]	−0.9 ± 0.2[b]	−1.0 ± 0.2[b]	−0.5 ± 0.2	−0.7 ± 0.1
Ponderal index (kg/m^3)	24.6 ± 0.5	23.1 ± 0.2[c]	23.0 ± 0.3[c]	23.4 ± 0.5	22.8 ± 0.5[b]	23.1 ± 0.4[b]

Values are mean ± SEM.

[a] No significant differences among SGA subgroups.

[b] $P < .05$; [c] $P < .01$; [d] $P < .001$; and [e] $P < .0001$ vs AGA-BRF.

intermediate between human milk and FOF2 and is rich in energy (4).

All 130 infants ended up remaining exclusively on BRF, FOF1, or FOF2 for a minimum of 5 months. Thereafter, solid foods (5–7 months) and follow-on formula (>6 months) were gradually introduced. Most of the original BRF cohort (61% of AGA; 56% of SGA) had stopped receiving BRF at age 8 months, and most of them (81% of AGA; 81% of SGA) had stopped receiving BRF at age 12 months.

Assessments

Weight and length were measured by the same investigator (GS) at birth, 4 months, and 12 months. Weight was measured with a beam balance (Seca, Hamburg, Germany) and length was measured with a board (Seca 207; Seca), the mean of 3 measurements being used for analysis.

Body composition was assessed by absorptiometry at 4 and 12 months with a Lunar Prodigy, coupled to Lunar software (version 3.4/3.5; Lunar Corp, Madison, Wisconsin), adapted for assessment of infants (4–6). Body fat, lean mass, and bone mineral content (BMC) were assessed during natural sleep. Coefficients of variation (CVs) were <3% for fat and lean mass (4–6).

Prefeeding levels of circulating glucose, insulin, IGF-I, and HMW adiponectin were measured in serum samples obtained, in the morning, at ages 4 and 12 months.

Serum glucose was measured by glucose oxidase method, and circulating insulin and IGF-I were measured by immunochemiluminescence (IMMULITE 2000; Diagnostic Products, Los Angeles, California). The detection limit for IGF-I was 25 ng/mL; intra-assay and interassay CVs were <10%. Insulin resistance was estimated from fasting insulin and glucose levels using the homeostasis model assessment. HMW adiponectin was assessed by ELISA (Linco Research, St Charles, Missouri) with intra-assay and interassay CVs <9%.

Statistics and ethics

Analyses were performed with SPSS 12.0 (SPSS, Chicago, Illinois). Age-adjusted and gender-adjusted Z-scores were calculated using mean and SD values from AGA-BRF girls and boys as reference (Supplemental Table 1). Skewed data were log-transformed before comparison. General linear models for repeated measurements were used to detect differences in 4-month and 12-month data and in changes thereof. The level of significance was set at $P < .05$. The study had 80% power to detect a difference of 0.6 SD between SGA-BRF and SGA-FOF infants. The detectable difference was 0.9 SD for comparisons between SGA-FOF1 and SGA-FOF2.

A previous report (4) focused on the interventional phase of this study (0–4 months). The present report focuses on the non-interventional follow-up (4–12 months) that was approved by the Institutional Review Board of Barcelona University, Hospital of Sant Joan de Déu.

Results

Table 2 provides the results in SGA infants, expressed in age-adjusted and gender-adjusted Z-scores, using the values in AGA-BRF controls (Supplemental Table 1) as reference; Supplemental Table 2 shows the same results, but expressed in absolute values, along with the pooled results of AGA-BRF girls and boys.

BRF infants: AGA vs SGA

The parallel control group of AGA-BRF infants disclosed that catch-up growth in SGA-BRF infants occurs in

Table 2. Results in SGA Infants

					P Values Among SGA		*P* Values vs AGA-BRF Reference (n = 31)		
	Column	SGA-BRF[a] n = 48 1	SGA-FOF1[a] n = 28 2	SGA-FOF2[a] n = 23 3	BRF vs FOF2 4	FOF1 vs FOF2 5	SGA-BRF 6	SGA-FOF1 7	SGA-FOF2 8
Length	4 mo	−1.28 (−1.52 −1.04)	−1.35 (−1.78 −0.92)	−1.14 (−1.61 −0.66)	.54	.50	**<.0001**	**<.0001**	**<.001**
	12 mo	−.26[d] (−.62 −0.10)	−0.40[c] (−0.68 −0.12)	0.03[d] (−0.52 0.58)	.37	.14	.33	.08	.93
Lean mass	4 mo	−0.39 (−0.78 −0.01)	−0.02 (−0.60 0.56)	−0.34 (−0.76 0.07)	.89	.38	.17	.95	.21
	12 mo	−0.52 (−0.99 0.06)	−0.61 (−0.99 −0.23)	−0.42 (−0.79 0.05)	.78	.48	.11	**.02**	.11
Fat mass	4 mo	−0.98 (−1.27 −0.69)	−1.27 (−1.77 −0.79)	−1.21 (−1.63 −0.80)	.35	.85	**<.0001**	**<.0001**	**<.0001**
	12 mo	−0.83 (−1.07 −0.59)	−0.58[c] (−0.98 −0.19)	−0.37[d] (−0.69 −0.05)	**.03**	.40	**<.0001**	**.03**	.14
Lean-to-fat ratio	4 mo	0.93 (0.40 1.45)	1.82 (0.80 2.84)	1.16 (0.58 1.73)	.59	.28	**.004**	**.002**	**.001**
	12 mo	0.66 (0.12 1.20)	0.58[c] (−0.35 1.50)	0.19[c] (−0.28 0.65)	.26	.47	**.04**	.22	.51
BMC	4 mo	−0.81 (−0.62 −0.10)	−0.35 (−0.83 0.14)	−0.39 (−0.92 0.14)	.12	.90	**<.001**	.24	.20
	12 mo	−0.40 (−0.76 −0.03)	−0.23 (−0.75 0.29)	0.02 (−0.32 0.36)	.10	.45	.14	.46	.94
IGF-I	4 mo	0.17 (−0.15 0.49)	1.12 (0.65 1.58)	2.38 (1.10 3.66)	**<.0001**	**<.05**	.50	**<.0001**	**<.0001**
	12 mo	0.37 (−0.12 0.85)	0.52 (−0.07 1.11)	1.28 (0.28 2.28)	.10	.18	.27	.13	**.008**
HMW adiponectin	4 mo	0.37 (0.01 0.73)	1.47 (0.70 2.24)	0.59 (0.12 1.29)	.53	.09	.17	**.001**	.11
	12 mo	−0.41[b] (−0.80 −0.01)	−0.25[d] (−0.90 0.40)	−0.88[d] (−1.41 −0.35)	.16	.14	.16	.48	**.005**
Insulin	4 mo	−0.25 (−0.50 −0.01)	0.38 (−0.28 1.05)	0.33 (−0.15 0.81)	**.02**	.89	.24	.29	.26
	12 mo	−0.41 (−0.59 −0.23)	−0.10 (−0.46 0.26)	−0.16 (−0.59 0.27)	.29	.81	.09	.69	.55
Glycemia	4 mo	−0.16 (−0.57 0.24)	−0.37 (−1.00 0.26)	0.14 (−0.33 0.60)	.36	.20	.57	.29	.63
	12 mo	−0.43 (−0.62 −0.23)	−0.32 (−0.61 −0.03)	−0.49 (−0.82 −0.15)	.75	.45	.09	.17	.06
HOMA-IR	4 mo	−0.28 (−0.51 −0.05)	0.43 (−0.32 1.18)	0.39 (−0.16 0.94)	**.03**	.94	.17	.28	.21
	12 mo	−0.43 (−0.60 −0.26)	−0.10 (−0.46 0.27)	−0.21 (−0.61 0.18)	.31	.65	**.04**	.70	.42

Significant differences are highlighted in bold.

[a] Values are Z-scores (mean and [confidence interval]) using age-specific and gender-specific norms from AGA-BRF controls.

[b] $P \leq .05$, [c] $P \leq .01$, [d] $P \leq .005$ vs 4- to 12-month change in AGA-BRF controls.

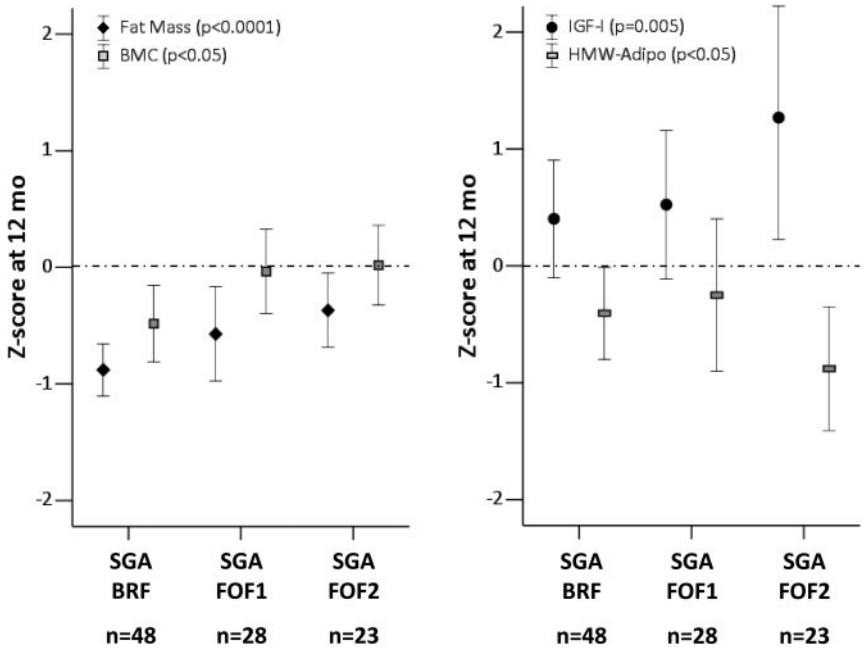

Figure 1. Z-scores of fat mass and bone mineral content (BMC) (left panel) and of circulating IGF-I and high-molecular-weight (HMW) adiponectin (right panel) at age 12 months in 99 small-for-gestational-age (SGA) infants, 48 of whom received breast-feeding (BRF) and 51 of whom received formula-feeding (FOF), either with a standard formula (FOF1; N = 28) or with a protein-rich formula (FOF2; N = 23) across early infancy. Confidence intervals are plotted. *P* values are from general linear models.

a sequence: the normalization of lean mass was mostly completed in early infancy (<4 months), whereas the normalization of bone mass (as judged by body length and BMC) continued into late infancy (4–12 months). Fat mass was still reduced and lean-to-fat ratio was still elevated at age 12 months, and this relatively hypo-adipose state was accompanied by a relative hypersensitivity to insulin and also by persistently normal levels of circulating IGF-I and HMW adiponectin (Table 2, columns 1 and 6).

SGA infants: BRF vs FOF

Catch-up in length continued into late infancy in all 3 SGA subgroups (Table 2, upper rows).

Between 4 and 12 months, SGA-FOF2 infants were characterized by catch-up of fat mass, by persistently elevated levels of circulating IGF-I, and by a striking fall of HMW adiponectin toward relatively low levels (Table 2, columns 3, 4, and 8).

The course of SGA-FOF1 infants was intermediate, their fat gain and HMW-adiponectin fall being comparable to those in SGA-FOF2 infants, but their IGF-I levels at 12 months being closer to those in SGA-BRF infants (Table 2, columns 2 and 7).

Figure 1 shows that, at age 12 months, SGA-BRF infants have a low fat mass and BMC but normal levels of IGF-I and HMW adiponectin, that SGA-FOF2 infants have a more normal fat mass and BMC but high IGF-I and low HMW adiponectin levels, and that SGA-FOF1 infants have intermediate outcomes.

Discussion

In late infancy, SGA-BRF infants combine a low adiposity and a high insulin sensitivity with normal IGF-I and HMW adiponectin levels. In contrast, SGA-FOF2 infants combine a normalized adiposity and insulin sensitivity with high IGF-I and low HMW-adiponectin levels. Results of SGA-FOF1 infants were intermediate. Given that the metabolic and cardiovascular perspectives are better for SGA-BRF than for SGA-FOF2 infants (2, 3), the present findings suggest that nutriceutical research for SGA infants (8, 9) may have to be redirected as to aim for a high insulin sensitivity and for normal IGF-I and HMW adiponectin levels rather than for a normal body adiposity in late infancy.

Our study appears to be the first with fully longitudinal data (including absorptiometric evaluations and endocrine assessments in fasting blood) over up to 12 months in AGA-BRF controls and in nutritionally divergent SGA subgroups, all of whom were assessed by the same investigators and methods in a single center. Given the virtual absence of similar studies, it is difficult to embed our integrated observations into previously reported evidence. Our insulin, IGF-I, and HMW adiponectin results, for example, are difficult to compare—but not incompatible—with the 12-month results from pioneering studies (10–12) wherein the duration of exclusive BRF varied widely among SGA infants (range 0–8 months), yet the results of those SGA infants were pooled.

A weakness of our study is the relatively low number of participants. Another weakness is that the nutritional patterns among the SGA subgroups continued to differ into late infancy, due to prolonged BRF in a minority of infants. Therefore, we are unable to infer to which extent the different outcomes between 4 and 12 months are attributable to nutritional differences in early infancy and/or to those persisting into late infancy.

Our IGF-I results at 4 months align well with the reports that AGA-FOF infants have higher IGF-I levels than AGA-BRF infants, particularly when receiving protein-

enriched FOF (13–16). In AGA infants, higher IGF-I levels in early infancy associate to more length gain–and not to more fat gain—in late infancy (14). This association may not apply to SGA infants, because SGA-FOF infants had higher 4-month IGF-I levels than SGA-BRF infants, but gained more fat—and not more length or more lean mass—in late infancy (Table 2). Therefore, we propose that IGF-I levels in SGA infants—and perhaps also in AGA infants—reflect not only somatotropic drive but also adipose-tissue expansion, just as they do in hyperphagic-obese children (with or without growth-hormone deficiency) after craniopharyngioma surgery (17).

Compared to AGA-BRF infants, the AGA-FOF infants gain more fat-free mass in early infancy and gain more fat mass in late infancy (18). Compared to SGA-BRF infants, the SGA-FOF infants gain a similar amount of fat-free mass in early infancy (4, 6) but are here shown to gain more fat mass in late infancy, so that their fat mass at 12 months is less reduced than that of SGA-BRF infants. The catch-up of fat in SGA-FOF infants may partly be driven by adiponectin, because this adipokine can enhance early lipogenesis (19) and because SGA-FOF infants have elevated levels of circulating HMW adiponectin at 4 months (4). Further studies in SGA-FOF infants will have to clarify the mechanisms underpinning the apparent parallelism between their late-infantile gain of fat mass and their late-infantile fall of HMW adiponectinemia.

None of the available nutrition options seems able to normalize the endocrine state as well as the body composition of SGA infants. Early adipogenesis may have been irreversibly reduced in SGA infants (20) by an interplay of factors that inhibit the prenatal differentiation of adipocytes, such as Pref-1 (21), and of factors that favor the postnatal recovery of fat-free mass. This view offers a rationale for aiming at the combination of a low adiposity and a normal endocrinology in SGA infants, as achieved with BRF but not with FOF2. In many countries, the prevailing opinion is still to promote rapid growth in SGA infants, also in a country like India where a third of all babies (thus about 8 million babies per year) are born with a low weight and where the sequence from fetal growth restraint to adult diabetes is highly prevalent (9). We anticipate that, in such countries, early BRF and/or acceptance of a low adiposity across infancy will prove to be the most cost-effective way of preventing diabetes in the next generation.

Acknowledgments

Address all correspondence and requests for reprints to: Lourdes Ibáñez, Hospital Sant Joan de Déu, University of Barcelona, Passeig de Sant Joan de Déu, 2, 08950 Esplugues, Barcelona, Spain. E-mail: libanez@hsjdbcn.org.

This study was supported by the Ministerio de Ciencia e Innovación, Instituto de Salud Carlos III, Madrid, Spain (PI08/0443).

F.d.Z. is a Clinical Investigator supported by the Clinical Research Council of the University Hospital Leuven. G.S., M.D., and L.I. are Clinical Investigators of CIBERDEM (Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas, Instituto de Salud Carlos III, Spain). A.L.B. is an Investigator of the I3 Fund for Scientific Research (Ministry of Education and Science, Spain).

Disclosure Summary: F.d.Z., G.S., M.D., M.D.G.-R., A.L.-B., and L.I. have nothing to declare.

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