Nutritional Factors That Affect the Postnatal Metabolic Adaptation of Full-Term Small- and Large-for-Gestational-Age Infants

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ABSTRACT. *Objective.* **To document metabolic adaptation to ex utero life in small- (SGA) and large-for-gestational-age (LGA) infants in relation to fetal nutrition and postnatal feeding practices.**

Methods. **In a prospective study, 65 SGA (≤second centile) and 39 LGA (≥98th centile) full-term infants were recruited. Anthropometry was performed within the first 48 hours. There was full support of breastfeeding and close clinical observation. Blood glucose and ketone body (kb) concentrations were measured prefeed for the first 7 postnatal days. Infants were exclusively breastfed (BF), breastfed with formula milk supplementation (FS), or exclusively formula milk fed (FF).**

Results. **Within the SGA group, a measure of "thinness," the midarm circumference/head circumference ratio, was significantly correlated to the number of episodes of blood glucose <2.00 mmol/L. Epoch (age at sampling) analysis in this group showed no difference in blood glucose levels across the different feeding groups but revealed a statistically significant greater kb concentration for infants who were exclusively breastfed. For SGA infants, the median peak kb concentration (peak kb) was significantly different for BF, FS, and FF groups. Multiple regression analysis for the SGA group demonstrated that peak kb concentration was negatively related to the volume of formula milk, independent of blood glucose levels and neonatal anthropometry. For LGA infants, low blood glucose levels were offset by kb concentrations equivalent to those observed in infants who were appropriate for gestational age.**

Conclusion. **Neonatal ability to generate kb when blood glucose values are low depends more on successful breastfeeding than on size for gestational age or neonatal nutritional status. Routine blood glucose monitoring of LGA infants with no additional risk factors is not necessary. Routine formula milk supplementation for LGA and SGA infants should not be recommended.** *Pediatrics* **2002;109(3). URL: http://www.pediatrics.org/cgi/content/full/109/3/e42;** ***small for gestational age, large for gestational age, breastfeeding, ketone bodies, hypoglycemia.***

ABBREVIATIONS. kb, ketone body; AGA, appropriate for gestational age; IUGR, intrauterine growth restriction; SGA, small for gestational age; LGA, large for gestational age; SDS, standard deviation score; BF, breastfed; FS, formula supplemented; FF, formula fed.

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Received for publication Apr 2, 2001; accepted Nov 7, 2001.

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Neonatal metabolic adaptation is the process whereby the fetus adapts from a continuous supply of intravenous glucose in utero to a fast-feed cycle and a diet based primarily on milk (fat). In the first few postnatal hours, blood glucose levels will normally decline.[1] This decline is usually self-limiting even in an infant who is not fed and cannot be considered pathologic. After this initial decline, there is usually a brisk ketogenic response to low blood glucose levels. This phenomenon is seen in many mammalian species and is known as "suckling ketogenesis."[2] There is evidence that these ketone bodies (kb) provide an alternative energy source for the neonatal brain,[3] but to date, there has been little study of the factors that influence production of kb.[4] Previous work by Hawdon and Ward-Platt[5,6] documented the normal kb response in infants who are appropriate for gestational age (AGA) and also showed that certain groups of vulnerable infants, such as term infants with intrauterine growth restriction (IUGR) or preterm infants, seemed unable, under some circumstances, to mount a kb response. These infants were thus doubly at risk, ie, low blood glucose levels with no alternative cerebral fuels. This study investigated neonatal adaptation in infants who were small for gestational age (SGA; at high risk of IUGR) in relation to both fetal nutritional status and postnatal feeding practices.

Concerns for the infant who is large for gestational age (LGA) stem mainly from a perceived "continuum of risk" associated with infants of mothers who have diabetes.[7] Pederson, in the 1950s, suggested that in pregnancies complicated by diabetes, maternal hyperglycemia might lead to fetal hyperglycemia, and so to fetal hyperinsulinism.[8] This in turn would result in macrosomia of the newborn. Elevated plasma insulin levels in these infants in the immediate postnatal period would lead to inhibition of gluconeogenesis, glycogenolysis, lipolysis, and ketogenesis, placing these infants at risk of low blood glucose levels with a paucity of alternative fuels. It has not yet been documented whether LGA infants whose mother does not have diabetes are similarly at risk.

METHODS

Patients

Sixty-five SGA and 39 LGA infants were recruited (Table 1). Of these, 58 SGA infants and 24 LGA infants had metabolic studies as in some instances, parents consented to anthropometry and clinical monitoring but declined consent for metabolic samples. All infants were full term, ie, >36 completed weeks' gestation,

TABLE 1. Nutritional Factors That Affect the Postnatal Metabolic Adaptation of Full-Term SGA and LGA Infants

	SGA	LGA
Number recruited	65	39
Metabolic results available	58	24
IVI for hypoglycemia alone	6	2
Other IVI	1	0
Number analyzed (metabolic results)	51	22
BF (%)	11 (22)	13 (59)
FS (%)	23 (45)	7 (32)
FF (%)	17 (33)	2 (9)

IVI indicates intravenous infusion.

healthy, and free of major congenital abnormalities. The SGA infants were on or below the second centile for birth weight, and the LGA infants were on or above the 98th centile. In this way, we hoped to select infants who were most at risk of abnormal metabolic adaptation. Sixty-one appropriately grown infants (birth weights between the 10th and 90th percentile) were randomly selected for comparison of perinatal variables as well as growth and neurologic variables on follow-up. The AGA group did not undergo metabolic studies, as normal values for the metabolic parameters presented have been previously established for this group.[6] Maternal, obstetric, and perinatal factors were recorded.

Anthropometry

Anthropometric measures were performed on each infant within 48 hours of birth, including head circumference, length, birth weight, mid-arm circumference, knemometry (knee–heel length), and skinfold thicknesses (subscapular, quadriceps, triceps). Birth weight, length, and head circumference standard deviation scores (SDS) were calculated using the British 1990 growth reference.[9] Mid-arm circumference and mid-arm circumference/head circumference ratio SDS were calculated using the formula SDS = (x − mean)/SD, where the mean for gestation is taken from normative data from Sasanow et al.[10] We performed anthropometry to enable us to distinguish infants who had experienced true IUGR from "small normal" infants.

Blood Sampling

Prefeed blood glucose monitoring was performed on both SGA and LGA infants as clinically indicated (at least 6 hourly within the first 24 hours and as indicated thereafter). A heel-prick sample was collected into a fluoride oxalate tube and analyzed for clinical purposes using a Yellow Springs instrument (2300 Stat Plus; Yellow Springs Instruments, Farnborough, Hants, UK). One hundred microliters of the same sample was immediately drawn using the Wiretrol System (Drummond Scientific Co, Broomall, PA) and placed in a 1.5-mL microcentrifuge tube containing 0.46 mol/L 5% perchloric acid and centrifuged in the cold. The supernatant was collected and frozen at −20°C.

Biochemical Assays

These samples were later analyzed by automated microenzymatic methods adapted for the Cobas Bio centrifugal analyzer at Great Ormond Street Hospital for Sick Children. Lactate and pyruvate were analyzed using the lactate dehydrogenase reaction, glucose was analyzed using hexokinase, acetoacetate and β-hydroxybutyrate were analyzed using β-hydroxybutyrate dehydrogenase, alanine was analyzed using alanine dehydrogenase, and glycerol was analyzed using glycerokinase and glycerol-3-phospate dehydrogenase. The endpoint in each case was a change in fluorescence at 450 nm attributable to reduction or oxidation of nicotinamide, adenine, and dinucleotide. Very low values (<0.001–<0.005 mmol/L) were reported as "below limits for detection." The kb concentration was obtained by summing the acetoacetate and β-hydroxybutyrate concentrations.

TABLE 3. Multiple Regression Analysis

	SGA	LGA
	P Value	*P* Value
Formula milk intake*	.002	.437
Formula milk intake†	.001	.187

* Dependent variable: kb concentration at minimum blood glucose concentration >24 hours. Independent variables: minimum blood glucose concentration; birthweight SDS; length SDS; mid-arm circumference/head circumference ratio; triceps, subscapular, and quadriceps skinfold thicknesses; formula milk intake.
† Dependent variable: peak kb. Independent variables: blood glucose concentration at peak kb; birthweight SDS; length SDS; mid-arm circumference/head circumference ratio; triceps, subscapular, and quadriceps skinfold thicknesses; formula milk intake.

Feeding Regimens

Infants were fed according to maternal choice. Breastfed infants were given formula supplementation on clinical grounds, such as persistent low blood glucose levels or evidence of dehydration, or at maternal request. Formula milk intake was recorded as milliliters/kilogram/day. There were 3 feeding groups: infants who were exclusively breastfed (BF), infants who received formula supplementation in addition to breastfeeds (FS), and infants who were exclusively formula fed (FF). Expert breastfeeding help and advice were enlisted when required from qualified midwives. A number of infants received intravenous treatment. Six SGA infants received intravenous dextrose for a low blood glucose value alone; 1 SGA infant received intravenous therapy for a low blood glucose value and a raised packed cell volume. Two LGA infants (both born to mothers with documented diabetes) received intravenous dextrose for low blood glucose values. Infants who received intravenous dextrose for whatever reason were excluded from metabolic analyses as the process of metabolic adaptation may be altered and delayed in this group. Therefore, of 65 SGA and 39 LGA infants recruited, metabolic results were available on 58 and 24, respectively; of these, 7 SGA infants and 2 LGA infants received intravenous treatment. Thus, the results of 51 SGA and 22 LGA infants were included in the final metabolic analysis (Table 1).

Clinical Observations

A single observer (L.dR.) performed close clinical observation of all study infants. All infants were assessed at least once a day until discharge. This included a prefeed blood glucose value, a weight, and a clinical and neurologic assessment, as well as an evaluation of feeding. In many instances, infants were reassessed 3 or 4 times during each 24-hour period. Continued support and reassurance were offered throughout the postnatal stay by the researcher (L.dR.).

Statistical Analysis

As kb concentrations have a positively skewed distribution (this is further compounded by reporting very low levels as "below the level of detection"), the values are log transformed or analyzed using nonparametric statistical tests. For avoiding the confounding effect of repeated measures, summary statistics, namely the peak kb concentration, the minimum blood glucose level, and the kb concentration at the minimum blood glucose

TABLE 2. Epoch Analysis: Number of Data Points Utilized

	SGA						LGA					
	0–4	4–12	12–24	24–48	48–72	>72	0–4	4–12	12–24	24–48	48–72	>72
BF	5	5	5	10	5	3	10	14	4	12	2	
FS	7	19	17	20	14	10	3	2	2	5	1	1
FF	13	13	6	15	7	2	2	1	1	2	1	1

TABLE 4. Maternal, Obstetric, and Perinatal Factors

	SGA	AGA	LGA	*P* (Compares SGA, AGA, LGA)	*P* (Compares SGA, LGA)
Number of infants	65	39	61		
Mean maternal height/cm (range)	160 (147–175)	165 (147–181)	165 (153–183)	<.001‡	.765‡
Median parity (range)	0 (0–7)	1 (0–2)	0 (0–5)	<.001§	<.001‖
Maternal smoking (%)	27 (42)	23 (38)	4 (10)	.003¶	.002¶
Maternal alcohol (units/wk) (range)	1.64 (0–10)	1.69 (0–14)	0.95 (1–5)	.241‡	.004‡
Socioeconomic group (%)				<.001§	.006‖
1	6 (9)	22 (36)	9 (23)		
2	13 (20)	20 (33)	13 (33)		
3	16 (25)	11 (18)	7 (18)		
4	4 (6)	2 (3)	3 (8)		
5	26 (40)	6 (10)	7 (18)		
Problems in pregnancy* (%)	20 (30)	14 (23)	14 (36)	.307¶	
Delivery (%)				.337¶	.752¶
Vaginal	35 (54)	23 (38)	21 (54)		
Cesarean	23 (35)	27 (44)	12 (31)		
Other	7 (11)	11 (18)	6 (15)		
Fetal distress (%)†	17 (26)	4 (7)	6 (15)	.012¶	

* Includes diabetes, maternal substance abuse, pregnancy-induced hypertension, maternal hypothyroidism on treatment; † 1 = minute Apgar ≤5 or cardiotocograph abnormalities suggestive of fetal distress plus the presence of meconium in the liquor; ‡ Analysis of variance/*t* test; § Kruskal-Wallis test; ‖ Mann-Whitney *U* test; ¶ χ^2 test.

level, were derived for each infant. Epoch analysis was also performed for blood glucose and kb levels, whereby each infant contributes 1 value to the mean/median shown for each epoch. When a infant was sampled more than once during an epoch, mean/median values of those samples were used (Table 2).

To determine whether a neonatal anthropometric marker of fetal malnutrition could predict the magnitude of the peak kb response, we then examined factors that could be expected to have an influence on peak kb production in a multiple regression analysis (Table 3). We analyzed LGA and SGA infant groups separately. Peak kb and kb at minimum blood glucose level were used as dependent variables. Birth weight SDS; length SDS; knemometry; mid-arm circumference/head circumference ratio; triceps, subscapular, and quadriceps skinfold thicknesses; concomitant blood glucose level; and formula milk intake were used as independent variables. Formula milk intake (mL/kg/d) was measured on the day when the peak kb or kb at minimum blood glucose was recorded.

Ethical approval for the study was granted by the joint UCL/UCLH Committees on the Ethics of Human Research. Informed consent was obtained from parents in the immediate postnatal period.

RESULTS

Perinatal Characteristics

Table 4 summarizes the maternal, obstetric, and perinatal factors for all infants. Comparing the SGA, AGA, and LGA infant groups, there were significant differences across the groups with respect to maternal height, parity, smoking, and parental socioeconomic group. This suggests an excess morbidity in the SGA infant group, which reflects findings in previous studies.[11,12] Problems in pregnancy were not significantly different between the groups. However, SGA, LGA, and AGA infants had different problems: there were 5 cases of maternal substance abuse in the SGA group, with none in the other groups. Also, there were 2 cases of maternal diabetes in the LGA group, with none among the SGA or AGA infants. Twenty-three infants were born to mothers with pregnancy-induced hypertension: 2 LGA infants, 9 SGA infants, and 13 AGA infants. No case of pregnancy-induced hypertension was diagnosed before 34 weeks' gestation. Pregnancy-induced hypertension and maternal substance abuse are not thought to result in specific problems related to blood glucose control in the neonate, except when they result in a growth-restricted infant. In addition, 2 mothers with infants in the LGA group were treated for hypothyroidism; both mothers were euthyroid during pregnancy, and no specific problems related to maternal hypothyroidism were noted in

TABLE 5. Anthropometry

	SGA	LGA
Birth weight/g (range)	2358 (1651–2840)	4446 (3690–5000)
Birth weight SDS (range)	−2.4 (−3.5→−1.7)	2.3 (1.7–3.5)
Length/cm (range)	44.0 (41.5–52.0)	52.8 (47.0–58.0)
Length SDS (range)	−1.8 (−3.9–0.4)	1.3 (−1.4–3.4)
HC/cm (range)	32.6 (29.6–35.4)	36.1 (34.0–39.0)
HC SDS (range)	−1.6 (−3.1→−0.2)	1.2 (0.04–3.8)
MAC/cm (range)	8.6 (6.8–10.8)	12.1 (9.0–14.3)
MAC SDS*	−1.8	3.3
MAC/HC ratio	0.26 (0.16–0.34)	0.34 (0.26–0.40)
MAC/HC ratio SDS*	−1.4	3.5
Knemometry/mm	113.8 (86.7–127.0)	144.0 (115.5–152.8)
Quadriceps skinfold thickness/mm	4.6 (3.0–7.4)	11.0 (6.4–15.0)
Subscapular skinfold thickness/mm	3.4 (2.4–5.2)	7.6 (4.4–11.2)
Triceps skinfold thickness/mm	3.8 (2.2–5.7)	7.9 (5.4–11.5)

HC indicates head circumference; MAC, mid-arm circumference.
* Data from Sasanow et al.[10]

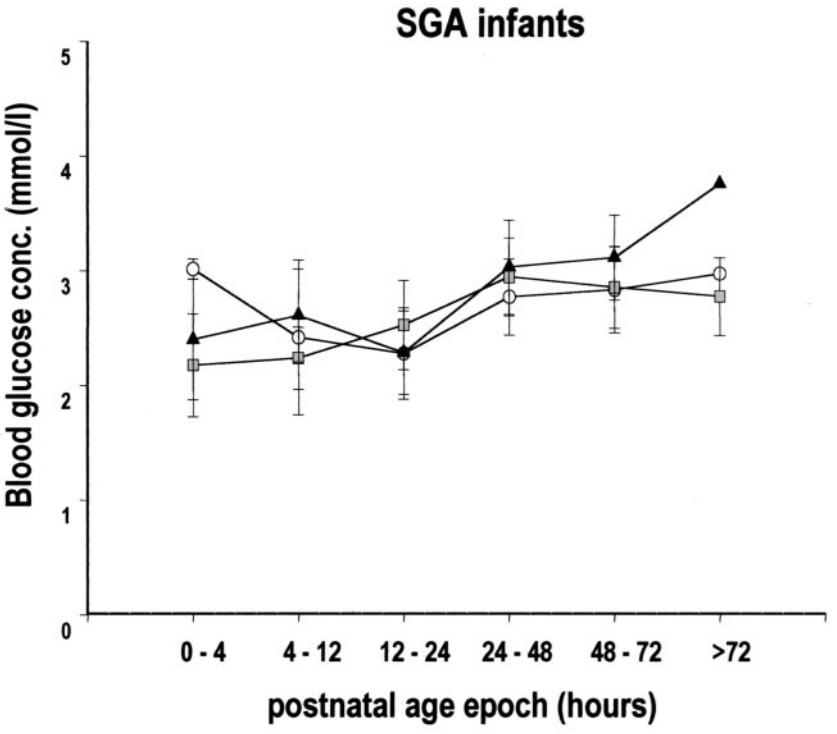
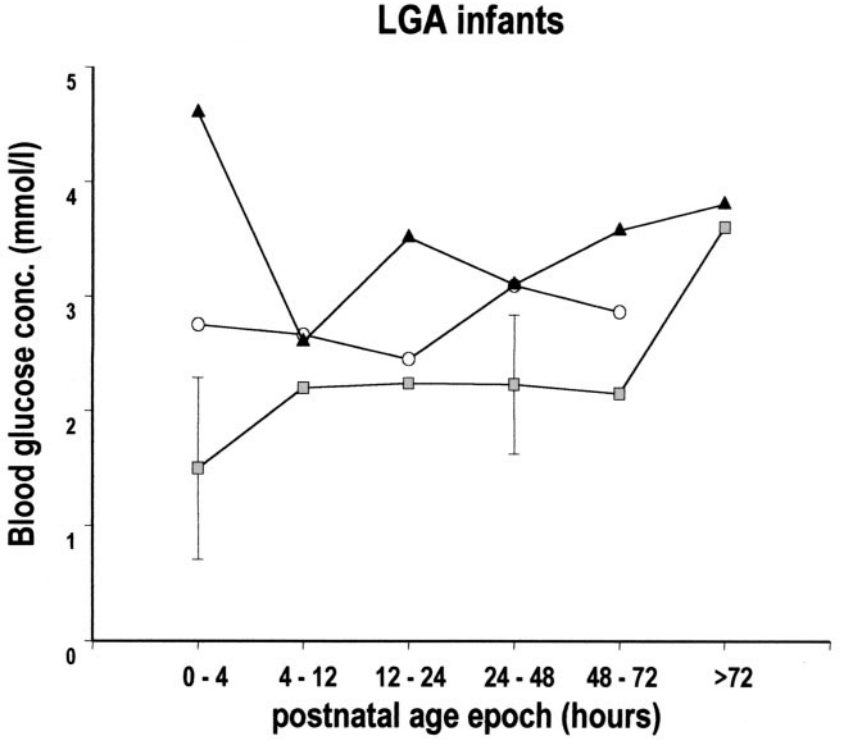


Fig 1. Blood glucose concentration versus postnatal age, SGA and LGA infants. ○, BF; ▨, FS; ▲, FF.



these infants. The number of cesarean deliveries was similar across the groups. Fetal distress (defined as a 1-minute Apgar of ≤5 or cardiotocographic abnormalities suggestive of fetal distress plus the presence of meconium in the liquor) was significantly different across the groups: 6 SGA infants were intubated as part of their resuscitation, compared with 3 LGA infants and 1 AGA infant.

Anthropometry

Anthropometry on all infants is shown in Table 5. A mean birth weight SDS of −2.4, with length and head circumference SDS scores of −1.8 and −1.6, respectively, indicates that the SGA group was underweight, with relatively preserved length and head growth. This is supported by other measures of

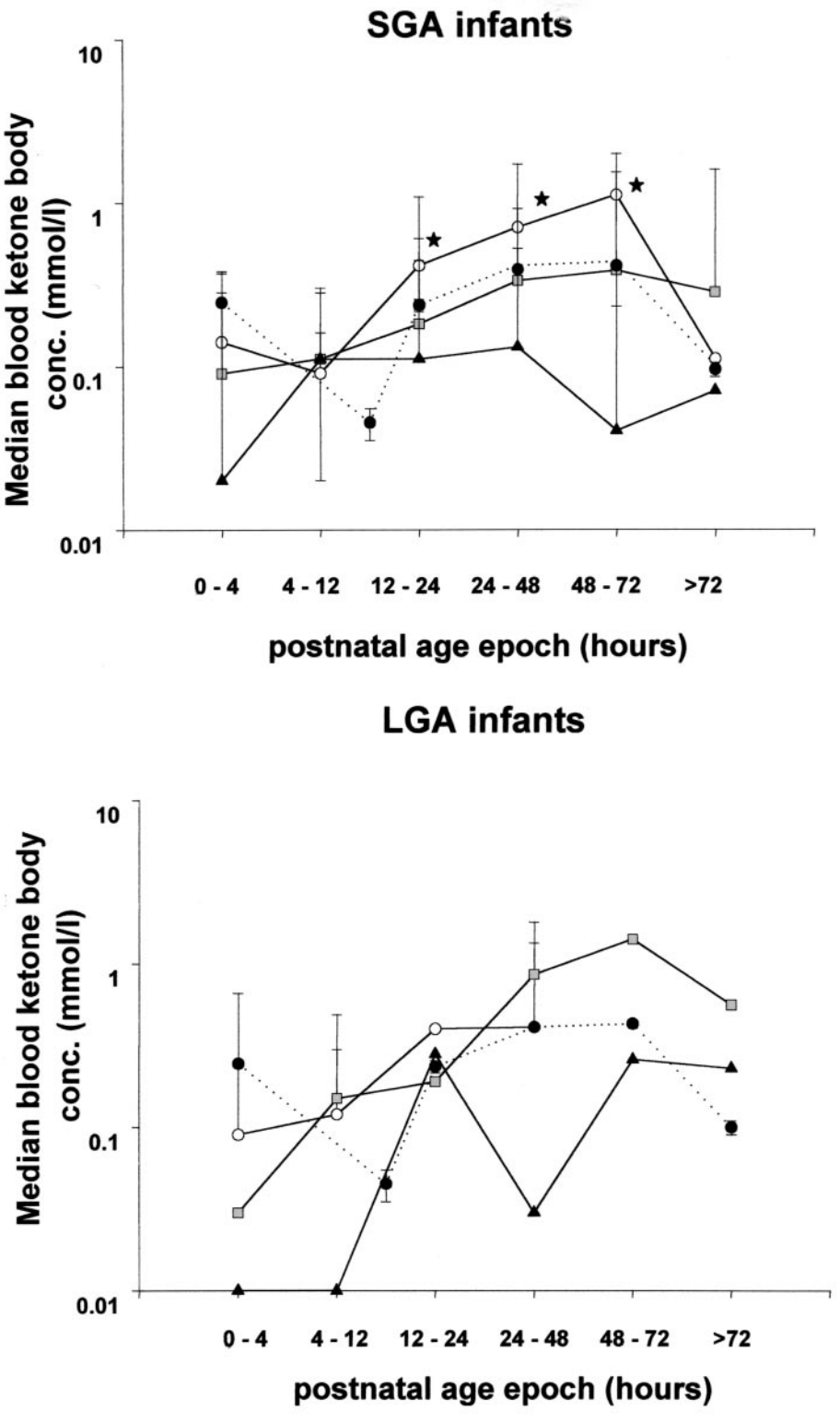


Fig 2. Kb concentration (mmol/L) versus postnatal age, SGA and LGA infants. ○, BF; ▨, FS; ▲, FF; ★, statistical significance; ●, AGA infants (Hawdon et al[6]).

thinness, such as the mid-arm circumference and the mid-arm circumference/head circumference ratio. Considerable overlap in the range of neonatal measures of intrauterine nutrition (eg, mid-arm circumference, skinfold thicknesses) indicates that even when using an exclusion criterion of ≤second centile, some small "well-nourished" infants have been included in the SGA group.

Metabolic Studies

Within the SGA infant group, a measure of thinness, the mid-arm circumference/head circumference ratio, was significantly correlated to the number of episodes of blood glucose <2.00 mmol/L (P = .025, Pearson's coefficient = −0.325).

The change in blood glucose levels over time for

the SGA and LGA infant groups is illustrated in the epoch analysis shown in Fig 1. No significant difference is shown in blood glucose values across different feeding groups for the SGA infants in any epoch, whereas for the LGA group, a much larger spread of blood glucose values is apparent, as illustrated for AGA infants in previous work.[6]

Figure 2 shows the change in blood kb levels over time for SGA and LGA infants. These data show that SGA and LGA BF infants achieve a rise in kb production, which was not consistently observed in FF groups. FS infants had an intermediate response. So, although blood glucose values remained equivalent across the feeding groups with time, kb levels were greatest for the BF group, especially the SGA infants. Significant differences in kb concentration between feeding groups is shown for SGA infants at 12 to 24, 24 to 48, and 48 to 72 hours (illustrated with stars). Blood ketone values for AGA infants (from Hawdon et al,[6] previous work) are shown for comparison.

Our summary statistic, median peak kb concentration (Table 6), is significantly higher in the BF group compared with other feed groups for the SGA infants analyzed separately. We further explored the relationship between the blood glucose concentration and kb response by finding the kb concentration at the lowest blood glucose level for each infant at >24 hours of age (Fig 3, Table 6). Especially at low blood glucose values, infants who receive breast milk show some of the highest values for blood kb concentration. Our data show that exclusive formula feeding does not necessarily protect against low blood glucose values. Hence, the SGA FF infant could be doubly at risk of both low blood glucose values with a reduced kb response. No BF infant had both low blood glucose and low kb levels. For LGA infants, low blood glucose values were offset by kb concentrations of the same order of magnitude previously demonstrated for AGA infants[6] (Fig 3).

In the multiple regression analysis (Table 3), no anthropometric measure was found to be significantly related to peak kb. Formula milk intake (mL/kg/d), however, remained significant for the SGA group after correcting for other biological variables, including blood glucose values (see "Methods").

DISCUSSION

Many studies concerned with IUGR are bedeviled by the problem of definition: fetal malnutrition and SGA are not synonymous. By using an arbitrary cutoff point within a population, some small normal infants will be included. In a study by Deter et al,[13] only 40% of infants with IUGR were SGA (<10th centile), where "IUGR" was defined using a specific neonatal growth assessment score. As with all normally distributed variables, individuals within the extremes of the distribution may be "normal" or may have entered this area by virtue of an underlying pathologic process.

Our anthropometric data show that even when using stringent weight criteria (≤second centile), small normal infants are still included in the group. However, in the SGA group, a measure of thinness, the mid-arm circumference/head circumference ratio, was significantly correlated to the number of episodes of low blood glucose values, confirming earlier work[14] and indicating that it remains important to identify those who are truly growth restricted. Clinical vigilance, supported by simple measures such as the mid-arm circumference/head circumference ratio, could be used to identify those infants who, although having a birth weight above 2.5 kg, are still "thin" and therefore at risk. Interventions such as screening for hypoglycemia, clinical observations, but more especially expert breastfeeding support could then be targeted to this group. A similar strategy could be used to exclude small normal infants from interventions.

Our data clearly illustrate that formula feeding does not protect against low blood glucose values for small infants. This is noteworthy, especially as most of our small FF infants were fed at 100 mL/kg/day from the first day. BF infants, however, had equivalent blood glucose values but an augmented kb response in the same order of magnitude as their AGA counterparts.[6] Is there a biologically plausible explanation for this finding?

Mammalian animal studies have shown that the postnatal induction of the enzymes involved in β-oxidation within the mitochondria requires the presence of long-chain fatty acids.[15] The carnitine palmitoyltransferase system, which controls movement of long-chain fatty acids into the mitochondria, represents a major rate-limiting step in ketogenesis in the suckling rat. Long-chain fatty acids play a pivotal role in the posttranscriptional regulation of carnitine palmitoyltransferase 1 during the immediate postnatal period. We speculate that a factor present in breast milk but absent in formula milk augments ketogenesis in human neonates in the same way. Carnitine is known to have a central role in β-oxidation of fats: it is responsible for the transport of fatty acyl-coenzyme A across the inner mitochondrial

TABLE 6. Median Peak kb and kb Concentrations

	Breast Milk	Breast and Formula Milk	Formula Milk	*P* Value*
Median peak kb concentrations (mmol/L)				
SGA	0.875	0.435	0.126	<.0001
LGA	0.406	0.844	0.0172	.057
kb concentrations (mmol/L) at lowest blood glucose >24 h				
SGA	0.770	0.380	0.055	<.0001
LGA	0.610	0.490	0.0151	.075

* Kruskal-Wallis test.

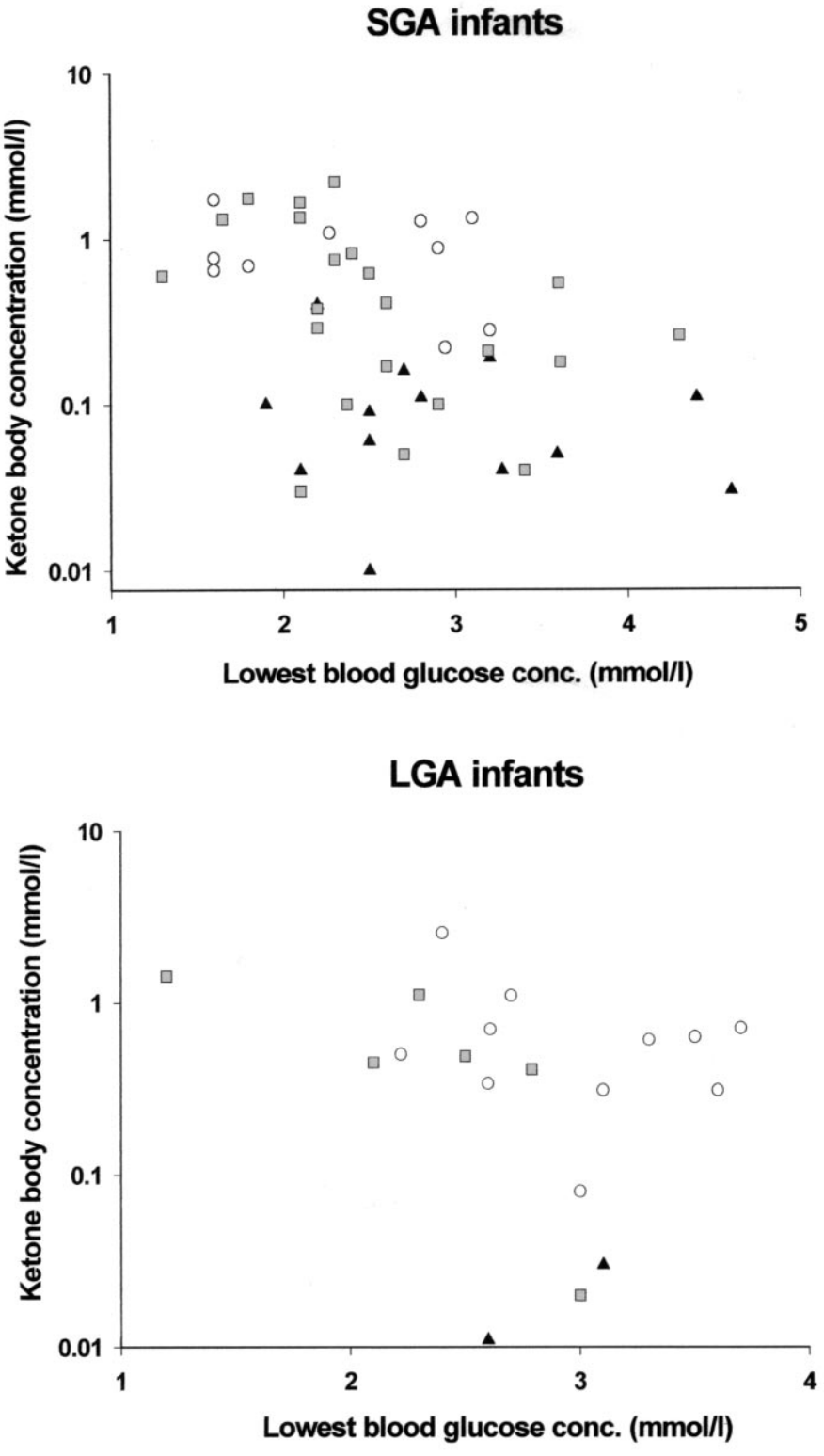


Fig 3. Kb concentration at lowest blood glucose at >24 hours postnatal age, SGA and LGA infants. ○, BF; ▨, FS; ▲, FF.

membrane.[16] During the suckling period, the demand for carnitine exceeds the rate of endogenous synthesis by up to 50%.[17] Indeed, healthy, full-term infants fed formulas devoid of carnitine showed reduction in ketogenesis and an accumulation of fatty acid precursors in the plasma. Although breast milk–and cow's milk–derived formulas contain equivalent amounts of carnitine,[18] it may well be that there are significant differences in bioavailability. When compared with breastfed control subjects, infants who were fed a standard formula that was not supplemented with carnitine demonstrated markers of carnitine deficiency.[19] Furthermore, we hypothesized that high intakes of energy and protein associated with early formula feeding may "switch off" or dampen the crucial glucagon surge, central to regulation of fuel availability in the immediate postnatal period.

Clinicians may fear[20] that a kb response in a neonate is indicative of "starvation," as in adult physiology. However, we argue that neonatal ketogenesis, as in many mammalian species, is a normal adaptive response that enables the transition from fetal to infant metabolism.

Multiple regression analysis showed that it was not possible to predict confidently the ability of a neonate to respond to the normal levels of low blood glucose found within the first few postnatal days with a kb response using anthropometric markers of thinness. Small, "fat" infants did not respond with higher kb peaks than small, "thin" infants. There may have been too little variation in the selected subgroups to demonstrate an effect, and this is something that could be usefully explored in additional work. However, infants who received breast milk alone consistently demonstrated an augmented kb response compared with FF infants.

LGA infants whose mother did not have documented diabetes do not represent a high-risk group. Although low blood glucose levels did occur, this was offset by a normal kb response, as previously shown for AGA infants.[6]

Any study that considers breastfeeding and the human neonate would do well to consider the sociodemographic factors that have an impact on breastfeeding patterns in the United Kingdom. Women who choose to breastfeed their infants are more likely to come from a higher social class and to be older than women who choose to formula feed.[21] Multiple antenatal insults, for example, substance abuse plus pregnancy-induced hypertension, were more likely in the SGA, FF group.[22] There is, to our knowledge, no known relationship between blood chemistry values and socioeconomic group, except as a proxy for growth restriction. Recognizing that adding a large number of variables may obscure a true association, we found no relation between blood glucose and mode of delivery or presence of fetal distress.

A "study effect" was noted: toward the end of the study period, midwives were confidently encouraging smaller infants to breastfeed, using the safeguards and protocols set in place for the study. Junior pediatricians and midwives worked together to admit, monitor, and safeguard the well-being of vulnerable infants on the postnatal ward, creating, in effect, a "transitional care" environment.

Breast milk is the food of choice for all newborn infants. Our data show that it is practicable, safe, and desirable to breastfeed even those infants previously considered to be at risk of abnormal neonatal adaptation, namely SGA and LGA infants.

ACKNOWLEDGMENTS

We thank Sally Lawrence and Suzanne Colsen for expert midwifery support throughout the study and Dr A. Williams and Prof M. Cornblath for critical review of the manuscript.

We gratefully acknowledge the assistance of the Department of Biochemistry at Great Ormond Street Hospital for Children NHS Trust for all metabolic assays.

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