Causes and Consequences of Intrauterine Growth Retardation in Latin America[1]

RAFAEL PÉREZ-ESCAMILLA[2] & ERNESTO POLLITT[2,3]

◆ ◆ ◆

The purpose of this article is to present a critical review of the literature on the causes and consequences of intrauterine growth retardation (IUGR) and of body proportions at birth among IUGR infants. IUGR is generally defined as a birth weight below the tenth percentile of a reference weight distribution according to gestational age. Chronic maternal malnutrition and other poverty-related factors are likely to be important determinants of IUGR in developing countries. IUGR has been associated with increased risks of neonatal morbidity and mortality and alterations in physical and mental development during early childhood.

IUGR newborns can be classified as "symmetric" or "asymmetric" in terms of body proportionality. The available literature indicates that the risk of perinatal morbidity is higher among asymmetric newborns than among their symmetric counterparts, while symmetric newborns confront a higher risk of impaired physical and mental development.

Obviously, the clinical and statistical usefulness of these IUGR and body proportionality assessments depends on the accuracy of the birth measurements (length, weight, and estimated gestational age) from which they are derived. Latin America now has the hospital infrastructure needed to obtain reliable birth data of this kind. It is important to use these resources effectively in order to improve the health assessment of newborns and gain a better understanding of the causes and consequences of IUGR.

I n 1980 the World Health Organization (WHO) estimated that 122.3 million children were born in the world every year. Of these, 20.6 million (17%) had low birth weight (<2,500 g) and 94% were born in developing countries. The average incidence of low birth weight was 18% in developing countries and 7% in industrialized countries (1).

Birth weight is an indicator of perinatal morbidity and mortality risk that is relatively easy to measure. However, by itself it is nonspecific, since it does not take into account the newborn's length or its gestational age.

Measurements of intrauterine growth retardation (IUGR) and Rohrer's ponderal index (PI) take the newborn's weight, height, and gestational age into account. For this reason there is a great deal of interest in using them to understand the etiology of IUGR and to identify newborns at risk of suffering disorders relating to physical and mental development.

The first aim of this article is to present a literature review concerned with the definition, statistics, causes, and consequences of intrauterine growth retardation, with emphasis on the situation in Latin America. The second aim is to present results of a recent analysis of data from a longitudinal study conducted in

[2]Nutrition Department, University of California at Davis. Mailing address: University of California at Davis, Nutrition Department, Davis, CA 95616, USA.
[3]Department of Applied Behavioral Sciences and Program of International Nutrition, University of California at Davis.

Guatemala describing the risks of physical development associated with IUGR during the first two years of life.

METHODS

To review the literature on the subject, articles were identified by means of the MEDLARS II electronic data banks. Nearly all the articles selected were reviews of the literature or reports of studies conducted in Latin America or industrialized countries that were published in English or Spanish between 1969 and 1991.

DEFINITIONS

The presence of IUGR is generally determined by a birth weight below the tenth percentile of a reference weight distribution according to gestational age (2). However, the concept applies only to babies born full-term (from week 37 to week 42 of gestation) (3). Newborns with IUGR can be subclassified as having symmetric or asymmetric IUGR, in accordance with their PI (weight × 100/length³) and with the PI reference curve designed by Lubchenco et al. (4).

Symmetric newborns with IUGR (known as type I IUGR) are those exhibiting a "normal" PI at birth and a proportional reduction in height, weight, and head circumference. Asymmetric newborns with IUGR (known as type II IUGR) exhibit a low PI, since a considerable reduction in weight relative to their length and head circumference can usually be observed.

STATISTICS ON IUGR

In developing countries, between 10% and 35% of the newborns typically suffer from IUGR. These represent a majority of the newborns with low birth weights. It has been estimated that in 1985 the number of children born with IUGR in Latin America totaled 2.8 million (5). In industrialized countries, it has been estimated that 11% of the newborns suffer from IUGR (6). Because this percentage is close to the percentage below the tenth percentile in the normal population's birth weight distribution, it is possible that these children do not suffer from IUGR but merely represent the lower end in the distribution of a population of healthy newborns.

The data in Table 1 suggest that between 49% and 87% of the newborns with IUGR in developing countries are born with symmetric proportionality, but that this tends to be true of lesser percentages (20% to 61%) of the IUGR babies born in industrialized countries.

Pathogeny

During the twenty-eighth week of pregnancy a normal fetus attains 30% of the weight and 71% of the stature that it will have at the end of gestation (5). With this in mind, it has been suggested that the period of gestation in which fetal malnutrition begins is a fundamental determinant of the type of IUGR from which the newborn will suffer (2, 7).

It seems likely that symmetric newborns are the result of fetal malnutrition throughout pregnancy. Studies conducted with experimental animals have shown that when malnutrition is induced over the entire gestation period, the offspring have symmetric proportionality at birth—and the cellular division in all fetal organs (including the brain) is reduced by 15 to 20% (8).

This kind of IUGR (type I), the sort found most frequently in developing countries, is closely related to conditions of poverty and chronic malnutrition of economically disadvantaged mothers (2, 6). Among the hypothetical pathogenic factors that have been suggested are high parity, a short birth interval, breast-feed-

Table 1. Percentages of IUGR newborn populations in developing and industrialized countries that were found to have symmetric body proportionality.

Country and (reference)	No. with IUGR	% symmetric
Argentina (urban middle class) (62)	54	61
Argentina (urban) (22)	495	49
Bolivia (urban) (24)	1,905	56
Guatemala (rural) (50)	97	78
Guatemala (rural) (26)	143	68
Guatemala (urban) (61)	848	79
Guatemala (urban middle class) (45)	3,398	87
Mexico City (24)	3,282	52
Philippines (urban and rural) (19)	241	61
South Africa (rural) (63)	188	67
Canada (69)	83	23
England (67)	47	34
England (68)	51	20
Netherlands (64)	119	61
United States (65)	33	39
United States (66)	165	20
Yugoslavia (70)	118	20

ing a prior infant during pregnancy, and low maternal weight gain during pregnancy. It has been pointed out that these factors can gradually deplete the mother's nutritional reserves (9–12) and, as a result, can prevent the fetus from receiving the necessary nutrients during gestation. However, more research is needed to confirm this theory.

During the 1970s a longitudinal study was conducted that involved supplementing the diets of mothers and children in four rural Guatemalan villages where moderate chronic malnutrition prevailed. The study's design and methods have been described elsewhere (13). Analysis of the study's results (14) supports the hypothesis of gradual maternal nutrient reserve depletion. More specifically, the mothers studied were classified retrospectively into three groups that received different supplements and a control group. One group of mothers, who received supplements during two pregnancies and lactation, had children with birth weights averaging 238 g higher

than those of children born to mothers in the control group. Indeed, the average weight of newborns in the former group was comparable to that reported for newborns in industrialized countries. Another group of mothers, who received supplements only during the previous lactation and pregnancy, had newborns with birth weights averaging 123 g higher than those of control group children. And finally, mothers who received supplements only during their latest pregnancy had newborns with birth weights averaging 113 g higher than those of the control group. Only the differences in weight between the control group and the group whose mothers received supplements during two pregnancies and lactation were statistically significant. These data suggest it is better to give supplements for long periods than to do so exclusively during short periods of pregnancy. It is possible that the differential response of birth weight to different durations of maternal supplementation might be explained by the need of a chronically un-

dernourished mother for a prolonged and gradual replenishment of her nutritional reserves.

It has been observed that smoking is associated with low birth weight (3), and it is possible that smoking throughout gestation could be associated with type I IUGR (5). Since smoking is an uncommon habit among women of reproductive age in marginal zones of developing countries, it is not considered an important determinant of type I IUGR in those populations. However, a study carried out in rural Guatemala (15) has indicated that large numbers of women were being chronically exposed to high concentrations of carbon monoxide produced by makeshift wood and coal stoves used inside poorly ventilated dwellings. (High environmental concentrations of this gas are associated with an increase in the concentration of carboxyhemoglobin in the blood of exposed people.) On the basis of the results of studies on smoking during pregnancy, the authors suggest that stove smoke could be an important determinant of IUGR in developing countries. Therefore, it is important to conduct studies on the effect of good ventilation on IUGR among marginal populations in developing countries exposed to high concentrations of carbon monoxide produced by makeshift stoves.

Two studies done in the United States (16, 17) have found that supplementation of the maternal diet was directly related to the birth weights of children born to smoking mothers. The effect was selective, since this phenomenon was not observed in a group of smoking mothers who received a placebo or among nonsmoking mothers. Although these studies need to be repeated in different populations before reaching a final conclusion, the results obtained suggest that smoking induces nutritional stress in the mother or the fetus during pregnancy.

A recent study conducted in Guate-mala City (18) also found helminthic infection of pregnant women to be associated with IUGR. This association persisted after factoring in various socioeconomic factors and the mothers' nutritional status. The study concluded that up to 10% of the observed IUGR cases could be attributed to infection of malnourished mothers by parasites.

Type II IUGR usually begins in the last trimester of pregnancy. For this reason, resulting growth retardation relates more to the newborn's weight than to its stature or head circumference. Hence, the newborn presents asymmetric proportionality at birth (being thin in relation to its stature and head circumference). This type of IUGR, the one most commonly found in industrialized countries, is probably related to late complications such as preeclampsia or infections occurring during the final weeks of pregnancy (2, 6).

Models Predicting IUGR Types I and II

An attempt has been made recently to develop mathematical models for estimating the probability that a baby will be born with type I or type II IUGR. Some models of this sort (19) have been based on maternal and neonatal factors such as the mother's place of residence, contact with health systems, maternal anthropometric data, habits such as tobacco use, maternal nutrition, parity, and the newborn's gender, gestational age, and anthropometric variables. One study, conducted in the Philippines, found residence in a rural area, low levels of adipose tissue in the maternal arm, smoking, low maternal stature, parity, and the gestational age of the newborn to be significant determinants of type I (symmetric) IUGR. However, only the last three factors had any effect on newborns with asymmetric proportionality. These results support the hypothesis that the fac-

tors determining body proportionality of IUGR newborns are different for symmetric and asymmetric newborns.

RISK FACTORS ASSOCIATED WITH IUGR

Morbidity

It has been reported that IUGR is associated with weaker cellular immunity during the first months of life (20, 21). Therefore, it is reasonable to suppose that IUGR increases the risk of infant morbidity.

In studies that have directly evaluated the relationship between IUGR and morbidity, it has been observed that IUGR increases the risks of being born with asphyxia, hypoglycemia, hypothermia, neonatal hyperviscosity (5, 22), hyperbilirubinemia (22), and birth defects (23).

Mortality

According to the results of a study (24) that analyzed clinical data applicable to 21,508 full-term babies in Mexico City, Mexico, and Santa Cruz, Bolivia, IUGR increased the risk of early neonatal mortality (death within the first three days of birth). In the Mexico City sample the relative risk (RR) was 2.1 (95% confidence interval 1.1–4.0) and in the Bolivian sample it was 3.7 (95% confidence interval 2.0–6.5). The fact that the lower limits of the 95% confidence intervals in the two populations were greater than 1 indicates that the difference in risks among newborns with and without IUGR was statistically significant in both countries. These results affirm the high risks of neonatal mortality associated with low birth weight that have been reported in both developed and developing countries (3).

Malnutrition

Using information contained in the data bank of a Guatemala-INCAP[4] study (13), the authors of this review used two strategies to compare the physical development of newborns with and without IUGR.

The first strategy consisted of comparing weight-for-age, weight-for-length (height), and length (height)-for-age at three-month intervals during the study children's first two years of life. This was done for each of these nutritional indicators by finding the z values at each three-month interval (the z value being the number of standard deviations by which the measure obtained in the children studied departs from the average expected in a healthy population—25). Comparisons were made for each of the three anthropometric indicators at each three-month interval using Student's t test. The three comparisons are shown in Figure 1.

The second strategy involved classifying the children according to the presence or absence of malnutrition, assessed on the basis of z values equalling or exceeding two standard deviations below the reference value for each growth indicator. The results of these analyses are presented in Tables 2, 3, and 4.

Weight-for-age, which does not distinguish between chronic and recent malnutrition, is not a very specific indicator. Length (height)-for-age is an indicator of chronic malnutrition, while weight-for-length (height) is an indicator of recent or acute malnutrition.

Application of the first strategy, using these three parameters, showed that the curve for the group with IUGR was always located below the curve for the con-

---

[4]Institute of Nutrition of Central America and Panama.

Figure 1. z value comparison of (a) weight-for-age data, (b) length-for-age data, and (c) weight-for-length data for AWGA and IUGR newborns. Bars represent the standard error of the mean; the value $z = 0$ corresponds to the 50th percentile of the reference distribution (see reference 25). The differences between the means for the AWGA and IUGR newborns were found to be statistically significant (Student's test, $p \leq 0.05$) at all ages except in the weight-for-length comparison, where the difference was found to be statistically significant at 15 days and between 15 and 24 months of age.
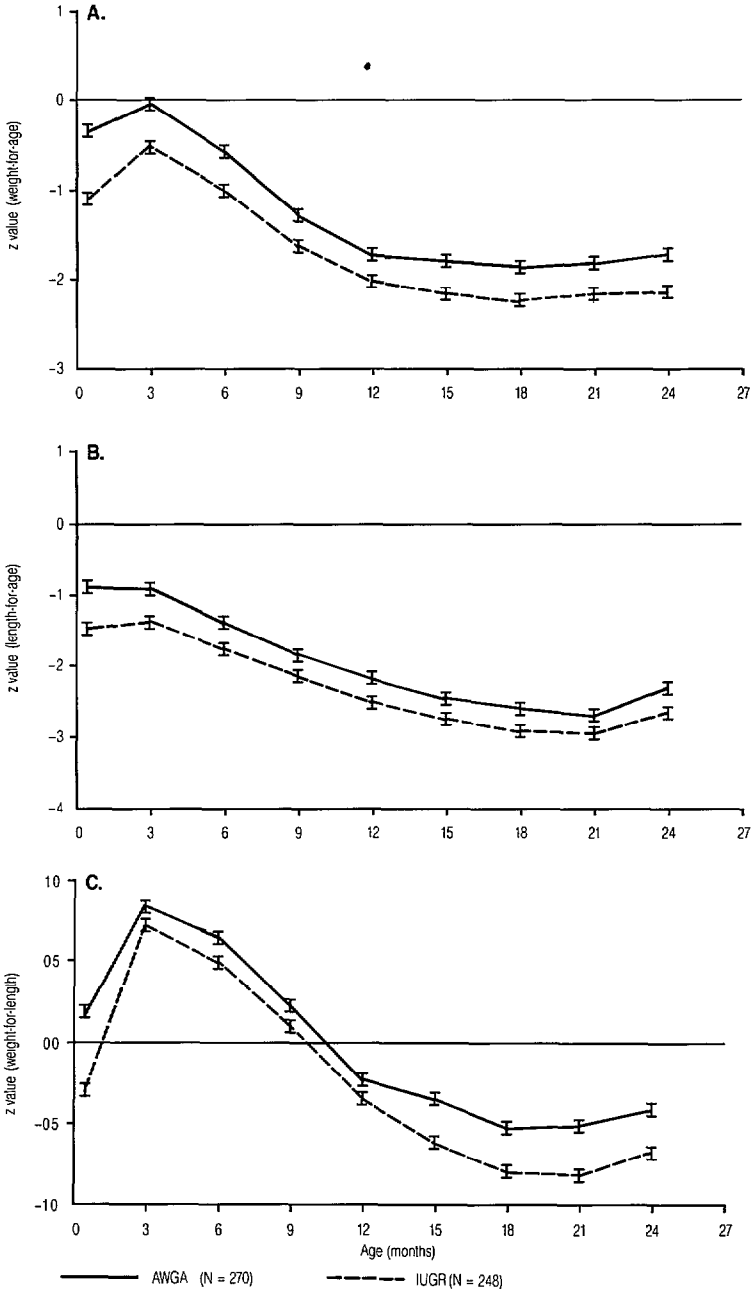
trol group (see Figure 1). The differences between the two groups regarding weight-for-age and length-for-age were statistically significant ($p < 0.05$) at every three-month age interval during the first two years of life. However, the differences regarding weight-for-length were statistically significant ($p < 0.05$) only at 15 days and 12 to 24 months.

Application of the second strategy indicated that malnutrition (based on weight-for-age) was significantly less prevalent in the control group, the proportion with malnutrition in this group being significantly lower than the proportion with malnutrition in the IUGR group at the ages of three months (56% versus 73%) and six months (79% versus 89%) (Table 2). After the latter age, no statistically significant differences were observed in the proportions of the two groups exhibiting weight-for-age malnutrition.

Similarly, the proportion of chronic malnutrition (low length-for-age) cases was significantly lower in the control group than in the IUGR group at three months of age (85% versus 95%) (Table 3), but after that age no statistically significant differences were observed.

Regarding recent (weight-for-length) malnutrition, the control group exhibited a significantly lower percentage of these cases than did the IUGR group at the ages of 15 months (76% versus 83%), 18 months (78% versus 89%), 21 months (81% versus 90%), and 24 months (79% versus 88%) (Table 4).

In sum, the two assessments showed the IUGR group to be at a disadvantage vis-à-vis the control group in terms of physical development and nutritional status over the first two years of life. These

Table 3. Rates of postnatal chronic malnutrition[a] found among Guatemala study children with adequate weight for gestational age (AWGA) and IUGR at birth, by age group.

Age (in mos.)	AWGA		IUGR		
	No.	%	No.	%	p[b]
3	231	85.5	236	95.0	≤0.05
6	262	97.0	246	99.0	>0.05
9	266	98.0	247	99.0	>0.05
12	269	99.0	248	100.0	>0.05

[a]As determined by a length-for-age at least 2 standard deviations below the 50th percentile length on the length-for-age curves of the U.S. National Center for Health Statistics (25).

[b]p = level of statistical significance indicated by the χ^2 test applied to the difference between the percentages of malnourished AWGA and IUGR newborns.

Table 4. Rates of postnatal weight-for-length malnutrition[a] found among Guatemala study children with adequate weight for gestational age (AWGA) and IUGR at birth, by age group.

Age (in mos.)	AWGA		IUGR		
	No.	%	No.	%	p[b]
3	63	23.3	72	29.0	>0.05
6	88	32.6	90	36.3	>0.05
9	144	53.3	134	54.0	>0.05
12	196	72.6	181	73.0	>0.05
15	204	75.6	206	83.1	≤0.05
18	211	78.1	221	89.1	≤0.05
21	218	80.7	222	89.5	≤0.05
24	213	78.9	218	87.9	≤0.05

[a]As determined by a weight-for-length at least 2 standard deviations below the 50th percentile weight on the weight-for-length curves of the U.S National Center for Health Statistics (25).

[b]p = level of statistical significance indicated by the χ^2 test applied to the difference between the percentages of malnourished AWGA and IUGR newborns.

Table 2. Rates of postnatal malnutrition (based on weight-for-age)[a] found among Guatemala study children with adequate weight for gestational age (AWGA) and IUGR at birth, by age group.

Age (in mos.)	AWGA		IUGR		
	No.	%	No.	%	p[b]
3	150	55.5	180	72.6	≤0.05
6	213	79.0	221	89.1	≤0.05
9	251	93.0	240	96.8	>0.05
12	261	97.0	246	99.0	>0.05

[a]As determined by a weight-for-age at least 2 standard deviations below the 50th percentile weight on the weight-for-age curves of the U.S. National Center for Health Statistics (25).

[b]p = level of statistical significance indicated by the χ^2 test applied to the difference between the percentages of malnourished AWGA and IUGR newborns.

results agree with those of another independent analysis of the Guatemala study that found IUGR newborns to be at a disadvantage—because at three years of age these IUGR children did not attain the weight, height, or head circumference of those born with adequate weight for gestational age (AWGA) (5, 26).

Mental Development

Infancy and Childhood

Based on data from the previously cited longitudinal study conducted in four Guatemalan villages, an analysis that included 405 children was conducted to study the effects of birth weight on neonatal psychomotor development and mental development up to six months of age (13). In order to study these effects, the Brazelton scale (N = 145) was used in the neonatal period and the composite infant scale (N = 352) was employed at six months of age.

In the neonatal period, an inverse relationship was observed between low birth weight and the tests of habituation, motor development, and state of alertness. In contrast, low birth weight was directly associated with tremors and sudden fright.

At the age of 6 months, an inverse relationship was observed between low birth weight and motor development. This significant association persisted after controlling for some 50 potentially confounding factors not specified by the authors. An inverse relationship was also observed between low birth weight and mental development; however, this latter association was not statistically significant.

In a study conducted in Puerto Rico (27), 37 newborns were classified according to stature, birth weight, and ponderal index. In cases where one or more of these parameters was below the tenth percentile of the distributions used, the newborn's fetal growth was considered abnormal (N = 15). When none of these parameters was below the tenth percentile of the distributions used, the newborn's fetal growth was considered normal (N = 22). When the newborns were evaluated using the neonatal behavior scale, the group with abnormal fetal growth received lower ratings than the control group in the areas of visual orientation, reflexes, and motor development, and also showed deficiencies in responsiveness and attention.

The PI was used as an indicator of the quantity of adipose tissue present. When the results were controlled for the PI, it was observed that the newborns with inadequate fetal growth showed deficiencies in their visual orientation, motor development, and autonomic nervous system. However, the other development deficiencies cited above disappeared.

The authors concluded that the factors which appeared when the results were controlled for adipose tissue reserves—such as the functioning of the autonomic nervous system—were attributable to nutritional deficiencies during the first trimester of pregnancy, while the factors that ceased to be statistically significant—such as state of alertness and responsiveness—were the result of nutritional deficiencies during the last trimester of pregnancy. The results of this study suggest that the effect of fetal malnutrition on the development of neonatal behavior is determined in part by the time at which malnutrition occurs; hence, these results support the hypothesis that the risks of particular deficiencies in behavioral development are related to body proportions at birth, which in turn are an indicator of the nutritional history of the fetus.

An analysis based on the Guatemala-INCAP study (28) examined the relationship between symmetric IUGR, postnatal growth, and cognitive development at

ages 3, 4, and 5. At ages 3 and 4 the sample included 76 children who at birth had adequate weight for gestational age (AWGA) and 41 classified as having had IUGR. On account of the design of the study, at age 5 information was available for only 46% and 54% of the AWGA and IUGR groups, respectively. Because of the similarity of these percentages in the two groups and of the anthropometric data for those participating at ages 3 and 4 and those not participating at age 5, the possibility of a participant selection bias altering the results was considered unlikely.

At age 3 an inverse relationship was observed between symmetric IUGR and cognitive verbal abilities after controlling for the effect of rate of growth during the first year of life, socioeconomic level, and interactions between IUGR and these two latter variables affecting cognition. At ages 3 and 4 it was found that as the severity of deficient postnatal growth increased, it became more likely that children born with IUGR would obtain a lower rating on the memory test relative to children born with AWGA.

Although this study confirmed that the children born with symmetric IUGR performed least well in tests of cognitive development (26), at age 5 no adverse effect of IUGR on mental development was detected. The authors concluded that the risk of IUGR being associated with poorer mental development declines as age increases. However, they also recognized the possibility that these results might be explained by the reduced statistical power of the age 5 results occasioned by the small size of the sample.

Adolescence

A recent analysis of the Guatemala-INCAP study (29) evaluated the mental development of 169 adolescents with IUGR and 177 adolescents with AWGA who served as controls. This involved administering a battery of psycho-educational tests that included measurement of the adolescents' literacy, ability to read letters (Inter-American reading series) (30) and numbers, and general knowledge and intelligence (Raven's standardized progressive matrixes) (31). After controlling for the effects of speed of growth during the first year of life and of the interaction between this variable and IUGR affecting mental development, no statistically significant differences were found between the IUGR and AWGA groups with respect to any of these tests. In contrast, all the test scores were found to be positively associated with the adolescent subjects' speed of growth during the first year of life.

The authors recommended caution in interpreting these results, since their analysis did not study the effect of the severity of IUGR on mental development. For example, if the fifth instead of the tenth percentile of the distribution of expected weight for gestational age had been the criterion applied in classifying newborns as having IUGR, different results might have been obtained.

There is a slight possibility of a participation or selection bias existing in this study, since 18% of the original sample members could not be included in the analysis for lack of childhood or adolescent data. However, such bias appears unlikely in view of the fact that rates of abandonment were similar in the AWGA and IUGR groups (34% and 32%, respectively), as were the socioeconomic and anthropometric characteristics of the participants and nonparticipants (Pollitt E, Gorman K, Metallinos-Katsaras E, personal communication, 1991).

In conclusion, analyses of the longitudinal Guatemala study suggest that the risk of mental development changes appearing in those born with IUGR declines as age increases. It is interesting to point out that, except in the case of children

who were extremely underweight at birth, the studies on low birth weight and mental development conducted in developed countries have reached the same conclusion (28). It is possible that mental development depends to a great extent on the environment in which the individual grows and not so much on intrauterine history.

Dietary Supplementation and Mental Health

If it is supposed that chronic malnutrition of mothers has a negative effect on the growth of the fetus and that the latter affects postnatal development, then it is reasonable to suppose that maternal and child food supplementation in populations with prevalent chronic malnutrition has a positive impact on postnatal development mediated by improved intrauterine growth. A summary is provided below of the methods and most important findings of several studies that have researched the association between supplementation of the maternal diet during pregnancy and the mental development of the children resulting from such pregnancy.

In Bogotá, Colombia, a study examined the effect of maternal and infant dietary supplementation on postnatal development of nursing infants (31, 32). The criteria for selecting study families included residence in a poor Bogotá neighborhood, an expectant mother who was less than six months pregnant, and a malnourished child less than five years old or malnourished children constituting half or more of the children in the home (for purposes of the study, malnutrition was defined as a weight less than 85% of the Colombian reference value for a given subject's age).

Dietary supplementation was based on weekly distribution at a local center of basic food items such as powdered milk, bread, and cooking oil. The maternal diet was supplemented during pregnancy and lactation. It was estimated that mothers consumed 133 kcal and 20 g of additional protein daily as a result of these supplements. Infants three to six months old received dietary supplements in a high-protein vegetable paste. After six months, their diets were supplemented with powdered whole milk.

The children's postnatal development was assessed by means of Griffith tests (34). These tests measure the progress of motor development, provide results in five subscales (social and personal behavior, development of diction and language, visual and manual coordination, locomotive coordination, and performance), and permit calculation of a general coefficient that incorporates the five subscale results. In addition, the Einstein test was used to measure cognitive abilities (35).

The study was designed to include six experimental groups varying in terms of the nutritional supplements and educational stimuli received and the chronologic times at which nutritional supplements were provided. The results discussed here were based exclusively on comparison of the control group, whose members did not receive stimulation or supplements, and the experimental group whose members (mothers and children) received supplements during pregnancy and lactation but did not receive educational stimulation. The analysis up to 18 months of age (N for both groups combined = 141) showed independent effects of supplementation in the calculated general coefficients and in the subscales of the Griffith tests. However, the magnitude of these differences was small (32). The results of the analysis up to age 3 (N for both groups combined = 187) were basically similar, with the exception that the nutritional supplements had a more marked effect on girls than on boys (33).

The two analyses indicated that the effect of dietary supplements on postnatal development declines as age increases.

In the Guatemala-INCAP study, pregnant or nursing mothers residing in four rural villages and their children were invited to participate in a food supplementation program. Participants in two of the villages received supplement in the form of a corn meal gruel containing 163 kcal and 11 g proteins per 180 ml. Participants in the other two villages received a cold drink without proteins that contained 59 kcal per 180 ml. Both the gruel and cold drink contained iron, vitamins, and minerals. The participants ingested the supplement, consumption of which was not limited, at a site in each village. The volume of supplement consumed by each individual was recorded.

To measure the supplements' effect on childhood mental development, subjects were classified according to whether the amount consumed was small, average, or large. In order to evaluate children's psychomotor development, the "composite infant scale" (36) was employed. The study indicated that the level of food supplementation was significantly associated with mental development (37). At the ages of 15 and 24 months a direct relationship was observed between the quantity of supplement administered and the children's mental and motor development. A statistical factor analysis suggested that the supplement in this study, as in the Colombian study, had a greater impact on motor functions than on cognitive or linguistic functions.

A comparative analysis that took into account both the Bogotá and Guatemala studies concluded that the observed positive effects of food supplementation on children's development were minimal, because of the great deficit produced by other factors in the development of individuals living in economically disadvantaged areas (38). This suggests that despite the demonstrated biologic effects of dietary supplements, dietary supplement programs may not be beneficial in the absence of social measures.

In New York City, an experimental research study examined the effects that dietary supplementation provided for poor Harlem mothers had upon the mental development of their children (39). The mothers were randomly assigned to one of three experimental groups receiving the following: (1) a diet high in calories and protein, or (2) a diet high in protein but low in calories, or (3) a placebo. The criteria for selecting mothers were an initial pregnancy weight of less than 110 pounds, delivery of a child with low birth weight at the end of the last pregnancy, and a low weight gain noted during the first prenatal visit or a low protein intake. The supplementation was started in the first trimester of pregnancy and ended after delivery.

The results were unexpected, in that the supplement was not found to have had any positive effects upon birth weight. At the age of one year the children of supplemented mothers and the control children showed virtually no differences in the ratings obtained on the Bayley scale in terms of mental and motor development (40). The test of visual habituation provided one exception, because on this test the children of the supplemented mothers performed better than the controls. However, results of this study should be interpreted with caution, since no absolute proof exists that the participating mothers had nutritional deficiencies in the first place (one account considered the mothers' nutritional status adequate—41). In short, the investigation's results demonstrate the importance of obtaining reliable base information before performing interventions.

A retrospective study conducted in Louisiana (42) detected notable differences between the level of intelligence of

brothers participating in the WIC Program (a U.S. Government program providing supplements to mothers, nursing infants, and children) during different periods (43). The average intelligence quotient (IQ) of 21 children who participated in this program during the prenatal period was 13 points higher than the average IQ of their brothers, who began participating after reaching one year of age. The intelligence tests were conducted at the ages of 76 and 106 months, respectively. The IQ difference was attributed to the younger brothers' program participation having lasted longer and having commenced during a critical time in their development. However, because of shortcomings in the study design and methods, the validity of that interpretation should be questioned. Specifically, the older brothers' IQs may have been lower because they were tested at a different age than their siblings (106 versus 76 months), after having been exposed for a longer period to an environment possibly capable of having a counterproductive effect on mental development. Thus, it should be recognized that the study methods and design do not permit the influence of dietary supplements upon IQ to be separated from the possible influence of environmental factors (44).

RISK FACTOR DIFFERENCES IN SYMMETRIC VERSUS ASYMMETRIC NEWBORNS

Because of their physiologic differences at birth, it is reasonable to suppose that symmetric and asymmetric newborns respond differently to the environment. It also is reasonable to assume that the postnatal risks they confront will vary with the age at which individual development is evaluated. In this regard, differences have been found between symmetric and asymmetric newborns with respect to the effects of maternal dietary supplementation (44), perinatal morbidity (22, 45), postnatal growth, and behavioral development (26).

Maternal Supplementation

A study conducted in Taiwan, Republic of China, found that newborns with risk factors for dysmorphic intrauterine growth benefited more from maternal dietary supplementation than those without such factors. The risk of dysmorphic growth was estimated on the basis of the PI relationship between brothers born before and after the beginning of maternal dietary supplementation. The results suggest the effect that dietary supplementation of pregnant women may have on the nutritional status of newborns depends on a number of fetal growth characteristics (38).

Early Neonatal Morbidity

A prospective study of 15,878 newborns in a Guatemala City social security hospital examined the effect of body proportionality at birth on neonatal morbidity (45). Regarding the PI of the 3,450 newborns classified as having IUGR, that of 12% was low, that of 27% was intermediate, and that of 59% was adequate. The asymmetric newborns (those with the lowest PI) were found to be at greater risk ($p < 0.05$) than those with an adequate PI of receiving a low Apgar score in the first minute after delivery (odds ratio = 2.0; 95% confidence interval 1.1–3.7), experiencing aspiration syndrome (odds ratio = 12.5; 95% confidence interval 3.9–40.8), and manifesting perinatal distress (odds ratio = 3.2; 95% confidence interval 1.4–7.5).

When the PI was analyzed as a continuous variable controlled in a multiple linear regression with birth weight, the PI was found inversely related to seven in-

dicators of neonatal morbidity. Of these, two associations—between PI and aspiration syndrome and between PI and presence of meconium in the amniotic fluid—were found to be statistically significant ($p < 0.05$). These results suggest that the risk of neonatal morbidity increases with the degree of asymmetry.

Another study, this one in the city of Rosario, Argentina, investigated differences in the risk of early neonatal morbidity among newborns with symmetric and asymmetric IUGR (22). The study sample consisted of 5,539 newborns delivered full-term at two hospitals. After adjusting morbidity for sex, birth weight, gestational age, and the hospital of birth, it was found that newborns with asymmetric IUGR ran greater relative risks of hypoglycemia, asphyxiation, and respiratory distress than did newborns with adequate weight for gestational age (AWGA). Also, both symmetric IUGR newborns (N = 243) and asymmetric IUGR newborns (N = 252) ran higher risks of hyperbilirubinemia than did the AWGA newborns. With respect to body symmetry at birth, it was observed that those newborns with asymmetric IUGR ran greater relative risks (adjusted for sex, weight, age, and hospital of delivery) of hypoglycemia (relative risk = 6.29; 90% confidence interval 1.03–38.37) and asphyxia (relative risk = 3.58; 90% confidence interval 1.17–10.89) than did the newborns with symmetric IUGR. No significant differences were observed between the newborns with symmetric and asymmetric IUGR regarding the risks of hyperbilirubinemia and respiratory distress.

In sum, these two studies conducted in urban areas of Latin America suggest that IUGR increases the risk of morbidity—and that among newborns with IUGR, asymmetric ones run a higher risk of early neonatal morbidity than do their symmetric counterparts.

Early Neonatal Mortality

It has still not been determined whether the risk of mortality in developing countries is different for symmetric and asymmetric newborns. As the data in Table 5 indicate, that is because the results of any given single study depend to a great extent on the criteria used to classify IUGR newborns and assess body proportionality.

A study mentioned earlier (24) which examined groups of children in Mexico and Bolivia found that asymmetric newborns had a higher risk of dying in the early neonatal period (the first three days after delivery) than did the symmetric newborns. The relative risk (RR) of neonatal mortality in the asymmetric babies was found to be 2.9 in Mexico (95% confidence interval 1.5–5.8) and 5.7 in Bolivia (95% confidence interval 3.0–10.7). The RR of early neonatal mortality in the symmetric babies was lower in both countries, being 1.4 (95% confidence interval 0.6–3.4) in Mexico and 2.0 (95% confidence interval 0.8–5.4) in Bolivia. The authors recommended caution in interpreting these results, since the RR confidence intervals for symmetric and asymmetric newborns overlapped, indicating that the observed differences were not statistically significant. Moreover, it was not possible to estimate the reliability of the anthropometric measures and estimated gestational ages employed.

The study's analysis used the tenth percentile of birth weight for gestational age—taken from a reference curve generated with data from U.S. and European populations—as the criterion for determining IUGR. The symmetry index was obtained from the tenth percentile of the PI corresponding to the gestational age distribution generated by Lubchenco (4).

The results of the Mexico City study were later analyzed again (46), this time using as the IUGR criterion a birth weight below 2,900 g or the tenth percentile of

Table 5. Differences in neonatal mortality risks found for symmetric and asymmetric IUGR newborns using different criteria to define IUGR and body proportionality at birth. (BW = birth weight, PI = ponderal index, L = length, %ile = percentile).[a]

Type of IUGR	BW < 10th %ile[b,c], PI < 2.25			BW < 2,900 g[d], PI < 2.25			BW < 10th %ile[d,e], PI < 10th %ile[d]			L < 10th %ile[d]		
	N[f]	RR[g]	95% CI[h]	N	RR	95% CI	N	RR	95% CI	N	RR	95% CI
Symmetric	1,723	1.4	0.6–3.4	1,380	2.0	0.9–4.1	329	4.6	1.9–10.8	112	21.9	12.6–37.7
Asymmetric	1,559	2.9	1.5–5.8	1,419	3.1	1.6–5.8	607	5.5	2.9–10.2	824	2.9	1.3–6.0
Symmetric and asymmetric	3,282	2.1	1.1–4.0	2,799	2.6	1.4–4.5	936	5.2	2.9–9.0	936	5.2	2.9–9.0

[a]Adapted from references 24 and 46. The data shown include only full-term newborns (children born after week 37 of gestation).
[b]See reference 24.
[c]Reference standards obtained by combining corresponding data for North American and European populations.
[d]See reference 46.
[e]Reference curves prepared by Lubchenco; see reference 4.
[f]N = size of study sample.
[g]RR = relative risk.
[h]95% CI = 95% confidence interval of the RR.

the distribution generated by Lubchenco of birth weight corresponding to a gestational age of 40 weeks, while using the same PI criterion as in the first analysis. Again, no significant differences were observed between the mortality risks of symmetric and asymmetric newborns (see Table 5). However, when newborn stature was used as a criterion of symmetry, the mortality risk of the symmetric newborns was found to be 10 times higher during the first three days of life than that of the asymmetric newborns. These results contradict the prior theory suggesting that asymmetric newborns have the higher mortality risk and strongly indicate that the criteria for determining IUGR and symmetry need to be selected carefully.

It will be necessary to conduct several investigations in order to shed light on the subject of classifying IUGR and body proportionality. Recently, Kramer et al. (47), on the basis of studies they conducted in Canada, suggested that PI is a reflection of the intensity of IUGR, and that this intensity rather than the PI is the factor responsible for the increased risk of neonatal mortality. This argument casts doubt on the hypothesis that PI is an indicator of the nutritional history of the fetus. The same group of researchers have suggested that the proportionality index should be based on birth weight and not gestational age, as has been done to date (48), and have further suggested (49) that the PI should be used as a continuous variable, given the fact that in their studies they did not find a bimodal distribution that justified use of the symmetric versus asymmetric classification. These authors stated that caution should be exercised in extrapolating their findings to developing countries. On account of the implications of their hypotheses, it is very important to study those hypotheses among disadvantaged populations living in developing countries.

Nutritional Status

The Guatemala-INCAP study found that asymmetric newborns experienced accelerated early gains in weight, length, triceps skinfold, and head circumference relative to symmetric newborns (26). The stature of children in the asymmetric group was found similar to that of normal controls during the three years the study lasted. The head circumference of children in the asymmetric group was also comparable to that of children in the control group up to 18 months; after that age, however, the speed of growth declined to the same level as that of children in the symmetric group. In contrast, the growth of symmetric newborns was not accelerated, and their height and weight remained below those of the control group children throughout the study.

A recent study conducted in Cobán, Guatemala (50), found that Vitamin A concentrations in blood samples taken from the umbilical cords of symmetric newborns weighing 2,300 g or less at birth were statistically lower than those found in umbilical cord blood samples from asymmetric newborns of similar birth weight.

Mental Development

Most studies done on this subject have made no distinction between the concepts of low birth weight and IUGR in symmetric and asymmetric newborns, which may account for some of the contradictions that appear in the literature (51).

The longitudinal Guatemala study (26) indicated that children three years of age who were born with symmetric IUGR had a smaller head circumference than children born with asymmetric IUGR or an adequate ("normal") birth weight (26). Knowledge tests (discriminating with regard to learning, memory, and vocabulary) found the scores of children in the

symmetric group to be lower than those of children in the asymmetric and normal groups. However, the asymmetric children received scores similar to those of the normal children in all the knowledge tests except one (the digits test, a subcomponent of the memory test) (52).

These findings should be interpreted with great caution. Analysis of the same data by Gorman and Pollitt (28) did affirm that children three years old who had been born with IUGR had the lowest intellectual performance; but this analysis also indicated that the differences in mental development observed between controls and those born with symmetric IUGR diminished over time and disappeared by age five. Also, the previously mentioned analysis by Pollitt et al. (29) detected no inverse relationship between asymmetric and symmetric IUGR and the mental development of study population members evaluated during adolescence.

ENVIRONMENTAL MODULATION OF IUGR'S MENTAL CONSEQUENCES

The medical model that defines a static, direct, and linear relationship between a pathogen and a disease is usually not applicable to describing individual development. Proof exists that the psychosocial effects of trauma experienced at an early age will depend on the trauma's nature and intensity, and on interactions with the environment where the individual develops. Interactive models that take account of the socioeconomic environment and nutritional factors in the postnatal period need to be formulated in order to understand the behavioral development involved (53, 54).

It has been reported from industrialized countries that the magnitude of cognitive development deficiencies among nursing infants with very low birth weights is largely determined by the postnatal environment (55). It is well-known that the relationship between trauma experienced in early life (such as IUGR), socioeconomic level, and long-term behavioral development has not been studied in developing countries. Moreover, it is reasonable to assume that in populations where endemic conditions of poverty and malnutrition exist, socioeconomic level does not play the same role that it does in industrialized countries. For example, a study conducted in Guatemala (56) found that an interaction existed between the socioeconomic level, nutritional status, and intelligence level of the children studied. In areas of extreme poverty, the children's nutritional status had no effect on the intelligence level, which was invariably low. But in areas with higher socioeconomic levels, the intelligence levels of children with better nutritional status were higher.

CONCLUSIONS

IUGR is synonymous with fetal malnutrition. In developing countries it is closely related to poverty and, very possibly, to chronic maternal malnutrition. In industrialized countries it is more closely related to various medical complications of pregnancy.

In general, adequate data on weight, size, and gestational age at birth are unavailable in developing countries, and so statistics on IUGR and ponderal index (PI) are very limited. This situation should change soon, because a large number of Latin American hospitals now have the infrastructures and advisory services needed to properly obtain and register the information required to identify newborns with IUGR and classify them according to their PI. In the case of home deliveries, simplified forms devised by CLAP-PAHO[5] exist for obtaining data on

[5]The Latin American Center for Perinatology and Human Development.

birth weight and other perinatal variables (57).

Of course, this information's worth will depend on good quality control over the taking of measurements and recording of data. Fortunately, procedures already exist for standardizing and maintaining good quality control over neonatal anthropometric measurements and estimation of gestational age. These procedures can be utilized in clinical research (58, 59) and in the continual monitoring of newborns (59).

It is important to consider body proportionality at birth in seeking to study and understand the risk that alterations will appear in the physical and mental development of newborns with IUGR. In this context the PI can be a very useful indicator, since it provides insight into the nutritional history of the fetus during pregnancy and permits classification of newborns with IUGR according to their body proportionality.

Use of this classification has led to identification of distinct risk factors because, as suggested by critical analysis of studies in Taiwan (44) and Guatemala (26, 45), important differences exist in the growth and development of symmetric and asymmetric newborns. Studies done by Mueller and Pollitt (43) and Villar et al. (26) indicate that asymmetric newborns are apt to fare better than symmetric newborns in the long run. However, works by Villar et al. (45) and Caulfield et al. (22) also indicate that neonatal morbidity among asymmetric newborns tends to be higher than among symmetric newborns.

The reason for this disagreement may relate to the chronologic times at which the risk factors were evaluated. Asymmetric newborns suffer from malnutrition during the last trimester of pregnancy and can therefore be at great risk of morbidity and mortality in the neonatal period. On the other hand, symmetric newborns may have suffered fetal malnutrition during the entire gestation period; and so they may have experienced reductions in both cell size and cell division. As a result, over the medium term symmetric newborns face a higher risk of disorders affecting their physical and intellectual development. These risk differences disappear over time, as a series of social, cultural, and economic factors become more important determinants of childhood development than IUGR. This latter circumstance can explain the findings by Gorman and Pollitt (28) and Pollitt et al. (29) indicating that the prognoses for mental development of symmetric and "normal" newborns at age five and during adolescence are very similar.

It is important to emphasize that the definition of symmetry and asymmetry based on the PI is an arbitrary one. As the works of Haas et al. (24) and Balcazar and Haas (46) have shown, if another classification criterion is used, opposite conclusions can be reached with data from the same study. Moreover, Kramer et al. have cast doubt on the usefulness of the PI as a dichotomous variable (47–49). It is very important to continue with studies in this vein with a view to better understanding the etiology of bodily dimensions' proportionality at birth and the risks posed for the individuals involved.

In recent times the scientific community has emphasized the need to develop methods permitting detection of IUGR during pregnancy (2, 60). However, the principal factors determining IUGR and body proportions at birth are still not fully known. In order to understand and prevent the adverse effects of IUGR, those factors need to be understood. The development of mathematical models capable of predicting IUGR and body proportionality at birth with sufficient sensitivity and specificity represents a first step in that direction (19).

Very little is known about how the en-

vironment interacts with the effects of IUGR and body proportionality upon the physical and mental development of people living in disadvantaged areas of developing countries. The evidence available to date indicates a critical need to conduct studies addressing this matter as soon as possible.

REFERENCES

1. World Health Organization. The incidence of low-birth weight: a critical review of available information. *World Health Stat Q.* 1980;33:197–224.

2. Lin CC, Evans MI. *Intrauterine growth retardation: pathophysiology and clinical management.* New York: McGraw Hill; 1984.

3. Martorell R, González-Cossío T. Maternal nutrition and birth weight. *Yearbook Phys Anthropol.* 1987;30:195–220.

4. Lubchenco LO, Hansman C, Boyd E. Intrauterine growth in length and head circumferences estimated from live births at gestational ages from 26 to 42 weeks. *Pediatrics.* 1966;37:403–08.

5. Belizán JM, Villar J. El crecimiento fetal y su repercusión sobre el desarrollo del niño. In: Cusminsky M, Moreno EM, Suárez-Ojeda EN, eds. *Crecimiento y desarrollo: hechos y tendencias.* Washington, DC: Pan American Health Organization; 1988:102–19. (Scientific publication 510).

6. Villar J, Belizán J. The relative contribution of prematurity and fetal growth retardation to low birthweight in developing and developed societies. *Am J Obstet Gynecol.* 1982;143:793–98.

7. Villar J, Belizán JM. The timing factor in the pathophysiology of the intrauterine growth retardation syndrome. *Obstet Gynecol Surv.* 1982;37:499–506.

8. Winick M, Brazel JA, Velasco EG. Effects of prenatal nutrition upon pregnancy risk. *Clin Obstet Gynecol.* 1973;16:184–98.

9. Jelliffe DE, Maddocks I. Ecologic malnutrition in the New Guinea highlands. *Clin Pediatr.* 1964;3:432–38.

10. Merchant K, Martorell R. Frequent reproductive cycling: does it lead to nutritional depletion of mothers? *Prog Food Nutr Sci.* 1988;12:339–69.

11. Merchant K, Martorell R, Haas J. Maternal and fetal responses to the stresses of lactation concurrent with pregnancy and of short recuperative intervals. *Am J Clin Nutr.* 1990;52:280–88.

12. Merchant K, Martorell R, Haas J. Consequences for maternal nutrition of reproductive stress across consecutive pregnancies. *Am J Clin Nutr.* 1990;52:616–20.

13. Lasky RE, Lechtig A, Delgado H, et al. Birth weight and psychomotor performance in rural Guatemala. *Am J Dis Child.* 1975;129:566–70.

14. Villar J, Rivera J. Nutritional supplementation during two consecutive pregnancies and the interim lactation period: effect on birth weight. *Pediatrics.* 1988;81:51–57.

15. Dary O, Pineda O, Belizán JM. Carbon monoxide contamination in dwellings in poor rural areas of Guatemala. *Bull Environ Contam Toxicol.* 1981;26:24–30.

16. Metcoff J, Costiloe P, Crosby WM. Effect of food supplementation (WIC) during pregnancy on birth weight. *Am J Clin Nutr.* 1985;41:933–47.

17. Rush D, Stein Z, Susser M. *Diet in pregnancy: a randomized controlled trial of nutritional supplements.* New York: Alan R Liss, Inc.; 1980.

18. Villar J, Klebanoff M, Kestler E. The effect of fetal growth of protozoan and helminthic infection during pregnancy. *Obstet Gynecol.* 1989;74:915.

19. Adair LS, Popkin BM. Birth weight, maturity, and proportionality in Filipino infants. *Hum Biol.* 1988;60:319–39.

20. Chandra RK. Fetal malnutrition and postnatal immunocompetence. *Am J Dis Child.* 1975;129:450.

21. Ferguson AC. Prolonged impairment of cellular immunity in children with intrauterine growth retardation. *J Pediatr.* 1978; 93:52–56.

22. Caulfield LE, Haas JD, Belizán JM, Rasmussen KM, Edmonston B. Differences in early postnatal morbidity risk by pat-

tern of fetal growth in Argentina. *Pediatr Perinat Epidemiol.* 1991;5:263–75.

23. Khoury MJ, Erickson JD, Cordero JF, McCarthy BJ. Congenital malformations and intrauterine growth retardation: a population study. *Pediatrics.* 1988;82:83–90.

24. Haas JD, Balcázar H, Caulfield L. Variation in early neonatal mortality for different types of fetal growth retardation. *Am J Phys Anthropol.* 1987;73:467–73.

25. National Center for Health Statistics. NCHS growth curves for children from birth to 18 years. Hyattsville, Maryland: US Department of Health, Education, and Welfare; 1977. (Publication (PHS) 78-1650).

26. Villar J, Smeriglio V, Martorell R, Brown CH, Klein RE. Heterogeneous growth and mental development of intrauterine growth-retarded infants during the first 3 years of life. *Pediatrics.* 1984;74:783–91.

27. Lester BM, García-Coll C, Valcárcel M, Hoffman J, Brazelton TB. Effects of atypical patterns of fetal growth on newborn (NBAS) behavior. *Child Dev.* 1986;57:11–19.

28. Gorman KS, Pollitt E. Relationship between weight and body proportionality at birth, growth during the first year of life, and cognitive development at 36, 48, and 60 months. *Infant Behavior Dev.* (In press).

29. Pollitt E, Gorman K, Metallinos-Katsaras E. Long term developmental consequences of intrauterine and postnatal growth retardation in rural Guatemala. In: *New directions in human development research: from expanded knowledge base to application. Vol. 1. Research and infant behavior and development: visions of the future.* Ithaca, New York: 1991:43–70. (Cornell Symposium Series).

30. Manuel HT. *Technical report tests of general ability and tests of reading, Interamerican series.* San Antonio, Texas: Guidance Testing Associates; 1967.

31. Raven JC, Court JH, Raven J. *Manual for Raven's Progressive Matrices and Vocabulary Scales.* London: HK Lewis; 1984.

32. Herrera MG, Mora JO, Christiansen N, et al. Effects of nutritional supplementations and early education on physical and cognitive development. In: Tuner RR, Reese HW, eds. *Lifespan psychology: intervention.* New York: Academic Press; 1980:149–84.

33. Waber DP, Vuori-Christiansen L, Ortiz N, et al. Nutritional supplementation, maternal education, and cognitive develop-

ment of infants at risk of malnutrition. *Am J Clin Nutr.* 1981;34:807–13.

34. Griffiths R. *The abilities of babies.* London: London University Press; 1954.

35. Corman H, Escalona S. *Stages of sensorimotor development: a replication study.* Merill-Palmer; 1969:351.

36. Lasky RE, Klein RE, Yarbrough E, Kallio KD. The predictive validity of infant assessments in rural Guatemala. *Child Dev.* 1981;52:847–56.

37. Klein RM, Arenales P, Delgado H, et al. Effects of maternal nutrition on fetal growth and infant development. *Bull Pan Am Health Organ.* 1976;10:301–16.

38. Joos SK, Pollitt E. Effects of supplementation on behavioral development in children up to age of two years: a comparison of four studies. In: Brozek J, Schurch B, eds. *Malnutrition and behavior: critical assessment of key issues.* Switzerland: Nestle Foundation; 1984.

39. Rush D, Stein Z, Susser M. A randomized controlled trial of prenatal nutritional supplementation in New York City. *Pediatrics.* 1980;65:683.

40. Bayley N. *Bayley scales of infant development.* New York: Psychological Corporation; 1969.

41. Haas JD. Nutrition during pregnancy. *Science.* 1981;212:804–05.

42. Hicks LE, Langham RA, Takenaka J. Cognitive and health measures following early nutritional supplementation: a sibling study. *Am J Public Health.* 1982;72:1110–18.

43. Pollitt E, Lorimor R. Effects of WIC on cognitive development. *Am J Public Health.* 1983;73:698–700.

44. Mueller WH, Pollitt E. The Bacon Chow study: effects of maternal supplementation on birth measurements of children account for the size of a previous (unsupplemented) child. *Early Hum Dev.* 1984;10:127–36.

45. Villar J, De Onis M, Kestler E, Bolaños F, Cerezo R, Berendes H. The differential neonatal morbidity of the intrauterine growth retardation syndrome. *Am J Obstet Gynecol.* 1990;163:151–57.

46. Balcazar H, Haas J. Classification schemes of small-for-gestational age and type of intrauterine growth retardation and its implications to early neonatal mortality. *Early Hum Dev.* 1990;24:219–30.

47. Kramer MS, Olivier M, McLean FH, Willis DM, Usher RH. Impact of intrauterine growth retardation and body proportionality on fetal and neonatal outcome. *Pediatrics*. 1990;86:707–13.

48. Kramer MS, Olivier M, McLean FH, Dougherty GE, Willis DM, Usher RH. Determinants of fetal growth and body proportionality. *Pediatrics*. 1990;86:18–26.

49. Kramer MS, McLean FH, Olivier M, Willis DM, Usher RH. Body proportionality and head and length 'sparing' in growth-retarded neonates: a critical reappraisal. *Pediatrics*. 1989;84:717–23.

50. Neel NR, Alvarez JO. Chronic fetal malnutrition and vitamin A in cord serum. *Eur J Clin Nutr*. 1990;44:207–12.

51. Pollitt E. Developmental impact of nutrition on pregnancy, infancy, and childhood: public health issues in the United States. *Int Rev Mental Retardation*. 1988; 15:33–80.

52. Klein R, Irwin M, Engle P, Yarbrough C. Malnutrition and mental development in rural Guatemala. In: Warren N, ed. *Advances in cross-cultural psychology*. New York: Academic Press; 1977.

53. Sameroff AJ, Chandler MJ. Reproductive risk and the continuum of caretaking casualty. In: Horowitz FD, ed. *Review of child development research (4)*. Chicago: University of Chicago Press; 1975.

54. Werner EV, Smith RS. *Kauai's children come of age*. Honolulu: University Press of Hawaii; 1977.

55. Hack M, Breslaw N. Biologic and social determinants of 3-year IQ in very low birthweight children. In: Vietze P, Vaughan HG, eds. *Early identification of infants with developmental disabilities*. Philadelphia: Grune and Stratton; 1988.

56. Johnston FE, Low SM, de Baessa V, MacVean RB. Interactions of nutritional and socioeconomic status as determinants of cognitive development in disadvantaged urban Guatemalan children. *Am J Phys Anthropol*. 1987;73:501–06.

57. Kestler E, Dorgan J, Sibrián R, Aquino O, Villar J. Epidemiologic identification of infants with low birth weight in urban areas of Latin America: I. Organization, population, and methodology of the Guatemalan perinatal study. *Bull Pan Am Health Organ*. 1987;21:369–76.

58. Villar J, Dorgan J, Menéndez R, Bolaños L, Pareja G, Kestler E. Perinatal data reliability in a large teaching obstetric unit. *Br J Obstet Gynaecol*. 1988;95:841–48.

59. Villar J, Kestler E, Pareja G. Measurement error in clinical perinatal data. *Am J Obstet Gynecol*. 1989;160:380–82.

60. Villar J, Belizán JM. The evaluation of the methods used in the diagnosis of intrauterine growth retardation. *Obstet Gynecol Surv*. 1986;41:187–99.

61. Villar J, Altobelli LC, Kestler E, Belizán JM. A health priority for developing countries: the prevention of chronic fetal malnutrition. *Bull WHO*. 1986;64:847–51.

62. Carroli G, Belizán JM. Unpublished document.

63. Woods DL, Malan AF, Heese HV. Patterns of retarded fetal growth. *Early Hum Dev*. 1979;3:257.

64. Walker FJ, Ramaekers LHJ. The ponderal index as a measure of the nutritional status at birth and its relation to some aspects of neonatal morbidity. *J Perinat Med*. 1982;10:42.

65. Crane JM, Kapta MM. Comparative newborn anthropometric data in symmetric versus asymmetric intrauterine growth retardation. *Am J Obstet Gynecol*. 1980; 138:518.

66. Miller HG, Hassaneim K. Fetal malnutrition in white newborn infants: maternal factors. *Pediatrics*. 1973;52:504.

67. Villar J, Belizán JM, Spalding J, Klein R. Postnatal growth of intrauterine growth retarded infants. *Early Hum Dev*. 1982;6: 265–71.

68. Harvey D, Prince J, Burton J, Parkinson C, Campbell S. Abilities of children who were small-for-gestational age babies. *Pediatrics*. 1982;69:296.

69. Low JA, Galbraith RS, Muir D, Killen H, Karchmar J, Campbell D. Intrauterine growth retardation: a preliminary report of long-term morbidity. *Am J Obstet Gynecol*. 1978;130:534.

70. Kurjak, et al. *J Perinat Med*. 1978;6:102.