BCG vaccination of full-term infants with chronic intrauterine malnutrition: influence of immunization age on development of post-vaccination, delayed tuberculin hypersensitivity

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To determine the effect of intrauterine growth retardation (IUGR) on the response to BCG vaccination, we evaluated the specific delayed tuberculin hypersensitivity of 57 full-term infants with symmetric IUGR (SGA or small for gestational age) and 52 full-term infants with normal intrauterine growth (AGA or appropriate for gestational age). The infants were evaluated using post-vaccination skin tests to tuberculin purified protein derivative (PPD) and tuberculin lymphocyte transformation tests. Using a positive response to the skin test as an indicator of delayed hypersensitivity, we found that the rate of response to BCG in the SGA and AGA groups was similar. A total of 65% of infants with IUGR responded to BCG vaccination. The response rate among SGA infants who were vaccinated at 5 days of age, about 26 days of age (weight ≥2500 g), 3 months of age, and 6 months of age was 68%, 47%, 69%, and 88%, respectively. The overall response rate for infants with no IUGR was 71%; the rate of response to BCG vaccination among this group was 52% (those vaccinated at 5 days of age), 90% (3 months of age), and 80% (6 months of age). Our data suggest that the immunogenicity of BCG vaccine is similar in term infants who have normal or abnormal intrauterine growth and the presence of IUGR should not be a reason for delaying BCG vaccination.

Introduction

Intrauterine growth retardation (IUGR) is a major public health problem in developing countries. As many as 2 million infants with low birth weight that is secondary to chronic fetal malnutrition are born every year in Latin America, where the incidence of low-birth-weight infants can be as high as 30% (*1*). Growth-retarded infants represent a highly heterogeneous group in terms of etiology, severity, and body proportions. The most prevalent type of IUGR in developing countries, symmetric or proportionate IUGR, probably results from a long-term growth-retarding process that begins early in gestation and may be caused by inhibition of cellular mitosis. Infants with symmetric IUGR are characterized by proportional reductions in weight, length, and head circumference (*2*). Asymmetric inhibition of fetal growth results from interference with growth later in gestation, and infants with this type of growth retardation typically have visceral wasting and decreased birth weight but relative preservation of length and of head circumference. A multiplicity of socioeconomic and other factors, chronic malnutrition, poor education, and poverty are strongly associated with the incidence of IUGR among the underprivileged populations of developing countries (*3*).

Globally, tuberculosis is a serious and highly prevalent infectious disease and remains a significant problem despite public health control efforts. In the developing countries of Africa, Asia and Oceania, the incidence of pulmonary tuberculosis is as high as 300 per 100 000. Also, reported rates for countries in South America range as high as 225 per 100 000 (in Bolivia), while 70 per 100 000 is more typical (*4*). In such countries, the factors associated with acquiring the infection and of developing tuberculosis are similar to those associated with the high rate of IUGR.

BCG vaccination is the mainstay of tuberculosis control programmes in most countries. Because BCG is effective in preventing the severe forms of childhood tuberculosis, e.g., meningitis and miliary tuberculosis (*5*), WHO recommends that BCG vaccine be administered as early as possible to children in countries where the disease has a high prevalence (*6*).

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Based on recommendations by the WHO Expanded Programme on Immunization (EPI) (*7*), developing countries have adopted the policy of vaccinating children as newborns and young infants.

BCG vaccination of infants who have IUGR is not contraindicated according to EPI recommendations (*8*). In most countries where BCG vaccine is routinely used, infants are vaccinated soon after birth, without regard to their intrauterine growth status. It is not known, however, whether the vaccine is as immunogenic or protective in infants who have IUGR compared with those whose intrauterine growth is normal. There are only few data about the immune response of infants with IUGR to BCG vaccination, but the findings suggest that their immunogenicity may be poor. Studies of BCG vaccination of full-term newborns with severe IUGR in India reported that the cell-mediated immune response to the tuberculin protein is deficient if the vaccine is administered within 48 hours of delivery or at 1 month of age (*9, 10*). Other studies of the immunocompetence of newborn infants with IUGR have reported conflicting results about their ability, compared with infants whose intrauterine growth is normal, to respond to antigens in lymphoproliferative assays (*11–13*).

The long-term morbidity and mortality rates for infants with IUGR are high (*14*) and are partly accounted for by their greater risk of developing serious infections, including tuberculosis. Because of the absence of data about the immunogenicity of BCG in infants with IUGR, it is not known whether current vaccination programmes in developing countries decrease the risk of serious tuberculosis among such infants. We have evaluated the immunogenicity of BCG vaccination at different ages for a group of full-term infants with symmetric or proportionate IUGR and a group of full-term infants with normal intrauterine growth in an urban Brazilian population, using skin testing and lymphocyte transformation tests to tuberculin antigen. Our findings may be useful for determining the efficacy of current BCG vaccination programmes for infants in developing countries.

Materials and methods

Study subjects

The study subjects consisted of 109 infants born at the University Hospital of Ribeirão Prêto, University of São Paulo, Brazil. For none of the infants was there a history or clinical evidence of antenatal, maternal, or fetal infection, or a past or recent history of active or indolent tuberculosis in the mother or other family members. No infants had congenital anomalies. None of the mothers had taken corticosteroids or immunosuppressive drugs during pregnancy and none were addicted to alcohol or other drugs. Some of the mothers (57%) had been vaccinated intradermally with BCG vaccine in their infancy. There was no information about the tuberculin status of any of the mothers.

The gestational age of the infants was assessed from information supplied by the mothers and from somatoneurological scores (*15*). Only full-term infants were included (gestational age, 37–41 weeks). The infants were classified on the basis of fetal growth, using birth weight for gestational age (*16*), while Rohrer's ponderal index (PI) ((weight in grams)/(length centimetres)^3) x 100) was used as a body proportionality criterion. Only infants with proportional or symmetric growth retardation (PI for gestational age >3rd percentile on the reference chart (*17*)) were included in the study. Depending on their fetal growth, the infants were classified as small for gestational age (SGA) (birth weight <5th percentile for gestational age and PI >3rd percentile on the reference charts) or appropriate for gestational age (AGA) (birth weight between 10th and 90th percentiles and PI >3rd percentile).

Most infants born in the university hospital are vaccinated with BCG at their first visit to the primary health care centre at 1–2 months of age. For the purpose of this study, 23 full-term AGA infants were randomly selected from healthy newborns in the hospital nursery and vaccinated before being discharged. A total of 33 infants with symmetric IUGR were also selected in the hospital prior to being discharged and were randomly assigned to be vaccinated with BCG either before 5 days of age or when they weighed 2500 g. To test the effect of age at BCG vaccination on the infant's ability to respond to the vaccine, we also enrolled a group of older infants who received their care in the university primary health clinics. These infants had not previously been vaccinated with BCG because either their parents had failed to bring them for vaccination or they had a condition that gave a temporary contraindication for vaccination. The older infants included 16 SGA and 19 AGA infants, who were vaccinated at 3 months of age, and 8 SGA and 9 AGA infants, who were vaccinated at 6 months of age.

The characteristics of the study population are summarized below.

Group I — SGA infants

A1 — full-term infants immunized within 5 days of birth (n = 16).

A2 — full-term infants immunized when their weight was ≥2500 g (n = 17).

B — full-term infants immunized at age 3 months ± 15 days (n = 16).

C — full-term infants immunized at age 6 months ± 15 days (n = 8).

Group II — AGA infants

A — full-term infants immunized within 5 days of birth (n = 23).

B — full-term infants immunized at age 3 months ± 15 days (n = 19).

C — full-term infants immunized at age 6 months ± 15 days (n = 10).

The procedures used were in accordance with the ethical standards of the university hospital's committee on human experimentation.

BCG vaccination and follow-up

All the infants were followed up monthly in the university hospital's neonatal and primary health care clinics. At these visits an interim history, including information about feeding, development, and previous illnesses was collected and the infants were measured carefully and examined. To identify those infants previously sensitized to tuberculin proteins, we performed skin tests on all infants, except those immunized by 5 days of age, using a tuberculin purified protein derivative (5 IU of PPD-RT23) prior to and 15 days after BCG immunization. The 15th day post-vaccination was chosen because sensitization to BCG does not usually occur until 20–30 days after vaccination. No positive reactions were found for any infant.

All infants were immunized intradermally in the right deltoid region with 0.1 ml of freshly reconstituted Moreau, Rio de Janeiro BCG strain (Fundacão Athaulpho de Paiva, Rio de Janeiro, Brazil). All the vaccinations were performed by a trained public health nurse, and the manufacturer's technical recommendations were followed.

Each infant was examined once every two weeks for 3 months to detect any possible adverse reaction to BCG vaccination, such as excessive ulceration, enlargement of axillary lymph nodes, suppurative lymphadenitis, or osteitis. None of the 109 infants had any adverse reaction, and all had the expected normal BCG reaction 4–6 weeks after vaccination and an easily identifiable scar after 1–2 months.

Evaluation of post-vaccination delayed hypersensitivity

Cutaneous tuberculin delayed hypersensitivity tests were performed 12–14 weeks after BCG vaccination on all infants using PPD-RT23 with Tween 80 (Statens Seruminstitut, Copenhagen). The standard intradermal method (Mantoux) was used. Each infant received 0.1 ml of inoculum containing 5 IU of PPD in the anterior aspect of the left forearm. The reactions were read 72–96 hours later by one trained individual. The reaction was expressed as the largest diameter of the induration (in mm).

The post-vaccination lymphocyte transformation test (LTT) was used to assess lymphocyte proliferation to tuberculin 12–14 weeks after vaccination. For this purpose, a previously described lymphoproliferation assay was used (*18*). The results were expressed as a stimulation index (quotient of the proliferation of cells stimulated and not stimulated by tuberculin).

Tests for both cutaneous delayed hypersensitivity and lymphocyte proliferation to the tuberculin protein were performed for each infant during periods when no clinical evidence of acute infection occurred for at least 1 week.

Analysis of data

The skin testing induration diameters and the lymphocyte proliferation stimulation indices were analysed using a non-parametric Kruskal–Wallis analysis. Bivariate comparisons of categoric data were carried out using χ^2 tests. A two-sided P value of 0.05 was selected as the level of statistical significance.

Results

Characteristics of the study subjects

The birth weights of the SGA babies lay in the range 1710–2400 g (median, 2170 g) and their lengths in the range 41.5–47.0 cm (median, 45.0 cm), while the comparable values for the AGA babies were 2650–3900 g (median, 3325 g) and 46.0–53.0 cm (median, 49.5 cm). The ponderal indices at birth ranged from 2.20 to 2.85 (median, 2.45) for the SGA infants and from 2.3 to 3.41 (median, 2.70) for the AGA infants. The birth weight, length, and ponderal indices at birth were similar for comparable subgroups in the two study groups. Infants in the I A2 subgroup were immunized at a mean age of 26 ± 2.3 days. There were no significant differences between group I and group II infants for the following: median gestational age (38.5 weeks versus 39.5 weeks, respectively); previous maternal BCG vaccination status (57% versus 43% vaccinated, respectively); and maternal parity (45% versus 55% primiparous, respectively). A significantly higher proportion of the mothers of IUGR infants smoked cigar-

ettes (62% versus 21%, P <0.05) or had chronic hypertension (37% versus 12%, P <0.05) than the mothers of AGA infants, but these variables were similar for the various subgroups in groups I and II.

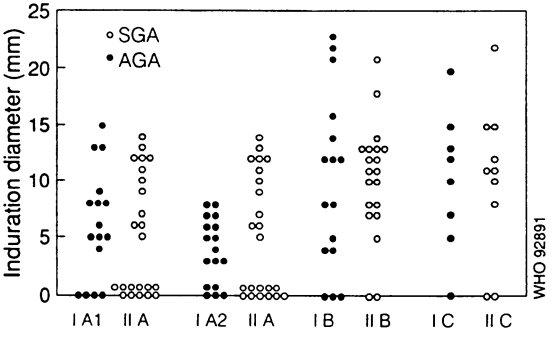
Infants in both groups I and II were well during the observational period, without recurrent infections or symptoms of respiratory infection. The proportions of infants who had been breast-fed before the post-vaccination testing were comparable for subgroups of similar immunization age (I A1 = 93%; I A2 = 78% versus II A = 77%; I B = 63% versus II B = 57%; I C = 22% versus II C = 30%).

Post-vaccination tuberculin skin testing reactions

The results of the cutaneous delayed hypersensitivity testing are shown in Table 1. The median induration diameter for SGA infants who were vaccinated when their weight was ≥2500 g (I A2) was significantly less than that for SGA infants vaccinated at 3 months of age (I B) or 6 months of age (I C) (P <0.05). Although the induration diameter for SGA infants immunized at birth was similar to that for infants who were not immunized until they weighed at least 2500 g, the differences between the SGA infants vaccinated at birth (I A1), 3 months of age (I B), or 6 months of age (I C) was not significant. The AGA infants vaccinated at birth (II A) had significantly smaller indurations than AGA infants vaccinated at 3 or 6 months of age.

An analysis of variance of the induration diameters (Fig. 1) in the skin tests for the two study groups did not reveal any significant differences between infants vaccinated at similar ages (I A1 versus II A, I B versus II B, I C versus II C). In addition, there was no significant difference between AGA infants immunized within 5 days of birth (II A) and SGA infants vaccinated when they weighed 2500 g (I A2); however, the frequency distribution of induration diameters in these two subgroups indicated a tendency towards smaller values among the SGA infants (I A2).

Fig. 1. **Post-vaccination skin test induration diameters in small-for-gestational-age (SGA) and appropriate-for-gestational-age (AGA) infants, vaccinated at comparable ages** (I = SGA, II = AGA; A and A1 = vaccinated within 5 days of birth; A2 = vaccinated when weight >2500 g; B = vaccinated at 3 months of age; C = vaccinated at 6 months of age).



Post-vaccination lymphocyte transformation tests

The infants' lymphocyte stimulation indices to PPD following immunization are shown in Table 2. There were no significant differences between the subgroups of SGA and AGA infants who were vaccinated at similar ages. Also, there were no differences in the stimulation indices of SGA infants who were vaccinated when they reached a weight of 2500 g and AGA infants vaccinated within 5 days of birth.

Correlation between skin test and lymphoproliferative responses

Comparison of 109 sets of post-vaccination skin reactions and stimulation indices for both study

Table 1: **Post-vaccination skin reactions to tuberculin PPD, according to intrauterine growth and age at vaccination**

	Age of SGA infants:[a]				Age of AGA infants:[b]		
	At birth	Weight ≥ 2500 g (26 days)	3 months	6 months	At birth	3 months	6 months
No. of infants	16	17	16	8	23	19	10
Median induration diameter (mm)	5.5 (0–13.8)[d]	3.5 [c] (0–7.2)	10.0 (0–21.5)	12.0 (0–15.5)	2.5 [c] (0–12.0)	11.0 (0–14.0)	11.0 (0–15.0)

[a] SGA = small for gestational age.
[b] AGA = appropriate for gestational age.
[c] P <0.05.
[d] Figures in parentheses are the 10th–90th percentiles.

Table 2: **Post-vaccination lymphocyte transformation indices to tuberculin PPD, according to intrauterine growth and age at vaccination**

	Age of SGA infants:[a]				Age of AGA infants:[b]		
	At birth	Weight ≥ 2500 g (26 days)	3 months	6 months	At birth	3 months	6 months
No. of infants	16	17	16	8	23	19	10
Median stimulation indices	1.8 (0.9–3.4)[c]	1.7 (0.9–2.8)	1.9 (1.0–3.2)	2.0 (1.1–2.9)	1.4 (0.9–2.7)	2.3 (1.4–3.6)	2.7 (1.6–3.8)

[a] SGA = small for gestational age.
[b] AGA = appropriate for gestational age.
[c] Figures in parentheses are the 10th–90th percentiles.

groups showed that there was a significant positive correlation between these variables (Spearman's rank correlation coefficient = 0.696; $P < 0.001$).

Indurations of diameter ≥5 mm and stimulation indices of ≥2.0 were defined as positive; this resulted in a 70% agreement between the variables. The discordant results were mainly from infants with a positive skin test and a negative stimulation index. Among the 75 children with an induration of diameter ≥5 mm and/or a stimulation index ≥2.0, only five (2 SGA and 3 AGA) would have been categorized as positive tuberculin reactors based exclusively on a positive stimulation index. All the remaining reactors had skin test induration diameters ≥5 mm. Thus, children who had a positive skin test were taken to be positive tuberculin reactors, irrespective of the results of the lymphocyte transformation tests. Table 3 shows the correlation between induration sizes and stimulation indices.

Tuberculin reactivity

The proportions of positive tuberculin reactors among the children immunized at similar ages are compared in Fig. 2; no significant differences were observed (I A1 = 68%; I A2 = 47% versus II A = 52%; I B = 69% versus II B = 89%; I C = 88% versus II C = 80%). As a group, 65% (37) of SGA infants and 71% (37) of AGA infants were considered to be positive responders. A larger proportion of infants in the younger subgroups were not tuberculin reactors (I A1 = 31%; I A2 = 53%; II A = 48%) compared with infants immunized when they were older (II B = 11%; I C = 12%; II C = 20%).

Discussion

Many factors are associated with IUGR in infants. To limit the effect of these variables on response to

Table 3: **Frequency distribution of stimulation indices in both groups of infants, according to induration diameter**

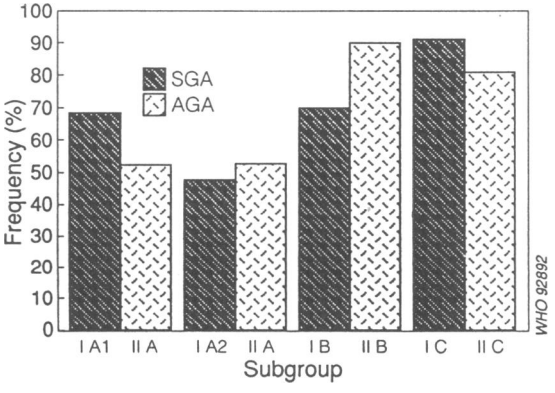
Induration diameter (mm)	Frequency at stimulation index range:							
	≤1	1.1–1.5	1.6–2	2.1–2.5	2.6–3	3.1–3.5	3.6–4	>4
0–1	11	12	4	2	1	—	—	—
2–3	—	1	1	1	—	—	—	—
4–5	—	3	9	1	—	—	—	—
6–7	1	2	3	2	1	—	1	1
8–9	—	2	4	2	—	2	—	1
10–11	—	1	1	2	2	2	2	—
12–13	—	1	3	6	3	2	—	2
14–15	—	—	1	1	1	2	1	2
16–17	—	—	—	1	—	—	—	—
18–19	—	—	—	—	—	—	—	—
20–21	—	—	1	—	—	1	—	—
22–23	—	—	—	—	1	1	—	1

BCG vaccination we included in the study only SGA infants with symmetric IUGR, because this selected for infants whose growth had most probably been affected early in gestation and whose immune systems may have had a greater effect on their development.

Post-vaccination tuberculin conversion has been correlated with the age of children at vaccination and with the type of vaccine used. In the present study, 52% of infants with normal intrauterine growth who were vaccinated as newborns had positive post-vaccination tuberculin reactions (Fig. 2). These results are comparable with those from other studies in Brazil that used a similar BCG vaccine in healthy newborns (*19*). As previously reported by other workers, we observed higher conversion rates for AGA infants who were immunized aged older than 1 month than for those immunized as newborns (*20–22*). This difference has been attributed to immunological immaturity of both lymphocyte and macrophage function.

There is evidence that a negative skin test does not necessarily imply absence of cell-mediated immunity to tuberculin (*23*). Both indicators were used initially to improve the sensitivity to detect positive tuberculin reactors. However, although there was a positive correlation between skin test reactivity and LTT results in our study population, the LTT used detected only very few tuberculin reactors. Thus, use of a positive response to either test would give similar results.

Fig. 2. **Post-vaccination positive tuberculin reactivity (skin test induration size ≥5 mm) in small-for-gestational-age (SGA) and appropriate-for-gestational-age (AGA) infants, vaccinated at similar ages** (I = SGA, II = AGA; A and A1 = vaccinated within 5 days of birth; A2 = vaccinated when weight >2500 g; B = vaccinated at 3 months of age; C = vaccinated at 6 months of age).



There was no significant difference in the post-vaccination delayed hypersensitivity of infants with and without IUGR who were vaccinated at comparable ages. This finding also resulted when the skin testing induration diameters and LTT stimulation indices were compared or if a positive limit was used in the skin test to identify tuberculin responders.

Previous studies of cell-mediated immunity, assessed using *in vitro* specific lymphoproliferation tests or delayed cutaneous hypersensitivity in newborns and older infants with IUGR, were unable to differentiate between these infants on the basis of the etiology or severity of their growth retardation (*24*). Studies in India have reported that the specific response to BCG administered after birth, as evaluated by post-vaccination skin testing, was significantly diminished in full-term newborns with severe IUGR (birth weights <3rd percentile or <1820 g), but was not significantly impaired in mild-IUGR infants (*9, 10*). In our series, eight newborns had birth weights <1820 g, but all had positive tuberculin reactivity after BCG vaccination. This difference in outcome for infants with severe IUGR may be attributed to either differences in the etiology or severity of intrauterine growth retardation for the different populations.

Recently there have been conflicting reports that transfer of tuberculin immunity from mother to infant during pregnancy may occur transplacentally or after birth (from maternal milk) (*25, 26*). Although we included the same proportion of vaccinated and nonvaccinated mothers in groups I and II, we did not know their tuberculin immunological status; the cell-mediated immune response measured for some infants may have been acquired passively either transplacentally or through maternal milk and therefore is an overestimate of the capacity of the infant to respond to BCG vaccine. This is not likely, however, since passively transferred maternal cell-mediated immunity usually declines in the 3 months after birth (*26*) and our earliest evaluation of the post-vaccination tuberculin reactivity was not performed until the infants were 12 weeks of age. Also the skin test results provided no evidence of prior sensitization to tuberculin protein. It is possible that passively transferred maternal immunity may have interfered with the development of immunity in the infant after immunization. The presence of maternal immunity may be a factor associated with the lower rates of response to BCG for infants vaccinated at birth compared with those vaccinated later.

Our findings confirmed that BCG vaccination is more immunogenic in older infants than newborns, but this age-associated difference applied to both healthy, term infants with and without IUGR. In addition, the rate of response to BCG vaccine in

infants with and without IUGR was similar for those who were immunized at comparable ages. Furthermore, we found no differences in the development of delayed hypersensitivity to BCG between infants with IUGR who were vaccinated at birth or when their weight reached 2500 g. No adverse reactions were observed for any infant, regardless of weight.

The presence of tuberculin hypersensitivity following BCG vaccination does not necessarily imply resistance to tuberculosis infection; however, cell-mediated immunity correlates with delayed-type hypersensitivity (*27*). The correlation between hypersensitivity and protection from tuberculosis as well as the interference of passively acquired cell-mediated immunity on early active immunization have not yet been explained. We conclude, however, that there is no reason to delay BCG vaccination of infants with IUGR. In developing countries that have a high prevalence of tuberculosis, early vaccination of infants with IUGR, a group that may be at increased risk of infection, could avoid the devastating consequences of the severe forms of the disease.

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Résumé

Vaccination par le BCG de nourrissons nés à terme et présentant un retard de croissance intra-utérine: influence de l'âge auquel la vaccination est pratiquée sur l'apparition d'une hypersensibilité retardée à la tuberculine

Dans les pays en développement, la tuberculose et les retards de croissance intra-utérine (RCIU) constituent des problèmes de santé publique et tout porte à croire que l'incidence des RCIU est liée à la pauvreté. Le type de RCIU le plus fréquent est l'hypotrophie due à des perturbations prolongées qui commencent au début de la grossesse et donnent des enfants dont l'hypotrophie est dite "harmonieuse". Ces nouveau-nés peuvent présenter un défaut de l'immunité à médiation cellulaire provoqué par des perturbations précoces de la différenciation et de la maturation du système immunitaire. L'OMS recommande aux pays dans lesquels il y a une forte prévalence de la tuberculose d'administrer en routine le BCG aux nouveau-nés et aux nourrissons, dans le cadre d'un programme de lutte antituberculeuse. Bien que le BCG ne soit pas contre-indiqué chez les nourrissons présentant un RCIU, on ignore s'il est aussi immunogène et protecteur chez eux que chez les enfants ayant eu un développement intra-utérin normal. On ne sait pas non plus si, chez les nourrissons atteints de RCIU, l'âge à la vaccination a une influence sur la réponse au BCG. Nous avons étudié les effets de l'âge auquel les enfants ont été vaccinés sur l'apparition d'une hypersensibilité retardée à la tuberculine chez 52 enfants nés à terme, normaux pour l'âge gestationnel et chez 57 autres enfants nés à terme, mais petits pour l'âge gestationnel et présentant une hypotrophie harmonieuse. Tous ces nouveau-nés provenaient d'une population urbaine du Brésil et ne présentaient aucun signe d'infection congénitale ou de maladie génétique. Les enfants normaux pour l'âge gestationnel ont été vaccinés à la naissance, à 3 mois ou à 6 mois; la plupart des enfants petits pour l'âge gestationnel ont également été vaccinés aux mêmes âges, mais un sous-groupe d'entre eux n'a été vacciné que lorsque les enfants ont atteint le poids de 2500 g. Pour évaluer l'hypersensibilité à la tuberculine, nous avons utilisé la réaction de Mantoux et un test de transformation lymphocytaire en présence de tuberculine; ces deux tests ont été pratiqués 12 à 14 semaines après la vaccination par le BCG. Leurs résultats ont été corrélés positivement, avec une concordance de 70%. La réactivité positive à la tuberculine, définie comme une réaction cutanée se présentant sous la forme d'une induration d'un diamètre supérieur ou égal à 5 mm, a été observée beaucoup moins souvent chez les nourrissons normaux pour l'âge gestationnel vaccinés à la naissance, que chez ceux vaccinés à 3 et 6 mois (52%, 90% et 80%, respectivement). Cette différence de réponse associée à l'âge avait déjà été rapportée par d'autres chercheurs. Un même taux de réponse associé à l'âge a été observé chez les nourrissons petits pour l'âge gestationnel vaccinés à la naissance ou par la suite, lorsqu'ils ont atteint 2500 g (68% contre 47%); ce dernier groupe a montré une réactivité sensiblement inférieure à celle des enfants vaccinés à 3 et 6 mois (69% et 88% res-

pectivement). Toutefois, les nourrissons normaux et ceux présentant un RCIU ont montré les mêmes taux de réponse lorsqu'on a analysé les données en fonction de l'âge auquel avait été pratiquée la vaccination. Aucun effet indésirable du BCG n'a été relevé dans aucun groupe. Les nourrissons atteints de RCIU répondent donc de la même façon à la vaccination par le BCG que ceux dont la croissance est normale et le fait pour un nouveau-né de présenter un retard de croissance intra-utérine ne doit pas retarder la vaccination par le BCG.

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