Low Birthweight Infants, Infection, and Immunity

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In this chapter, I will examine whether infants of low birthweight (LBW) are more susceptible to infection and to death from infection, than infants of adequate birthweight (ABW), and briefly compare their immunocompetence. As more than 90% of LBW infants are born in developing countries, the focus is on diarrheal and respiratory infections, measles, and malaria, which are major causes of childhood illness and death in these populations. LBW infants are estimated to comprise 16% of global births, so any increased susceptibility to illness or death among them is of public health relevance.

HETEROGENEITY OF LOW BIRTHWEIGHT INFANTS

The definition of LBW is a weight less than 2,500 g at birth and embraces newborns who differ in their maturity, body proportions, and composition, and in their physiologic and metabolic make-up. LBW infants can be divided into two broad subgroups: those born preterm (< 37 weeks’ gestation) and those who are growth retarded in utero and are born small-for-gestational age (SGA). In developed countries, most LBW infants are the result of a preterm delivery and are appropriately grown. In contrast, in low-income populations with high prevalences of LBW, intrauterine growth retardation (IUGR) is the major cause.

Visible differences in body size and body proportions are clearly evident among IUGR newborns. Fetal linear growth occurs mainly in the first 28 weeks of gestation (1), and chronic undernutrition and other adverse influences in early fetal life result in proportionate reductions in skeletal and soft tissues. Such infants are typically stunted at birth, but are not wasted. As the immune system starts to develop in early fetal life, and as an adverse fetal environment can permanently alter gene expression, organ structure, cell number, and hormonal responses (2), a differential impact of
LBW on immune function can be expected, depending on the causation, timing, and severity of fetal growth impairment. Thus, it is plausible that stunted LBW infants will be more susceptible to infectious disease than wasted or preterm LBW infants, and that any differential susceptibility may extend not only into childhood, but also into adulthood. In this chapter, in addition to comparing the relative risk of infection in LBW and ABW infants, I shall also explore evidence for a differential susceptibility among LBW infants.

LOW BIRTHWEIGHT AND INFECTION IN INFANCY AND EARLY CHILDHOOD

Risk of Death

Large population-based studies of birthweight-specific mortality consistently show an increased risk of neonatal and postneonatal mortality for both preterm and term LBW infants (3). Such studies are facilitated by computerized systems of linked birth and death records, which are rarely feasible in low income countries. For specific causes of death, few data sources disaggregate by birthweight and those that do tend to be small, community based studies. Table 1 presents the relative mortality risks in LBW infants compared with ABW infants for diarrhea (three studies), respiratory infections (four studies), infections other than respiratory or diarrhea (two studies), and all infections combined (one study) (4–17). Predominant among other infections were meningitis, sepsis, and measles. Studies of all-cause mortality have been included if infections were reported to comprise a large proportion of deaths (seven studies).

Although in only two studies were confounding variables controlled (4,13), the data are consistent with an increased risk of death from diarrheal, respiratory, and other infections during the first year of life in LBW infants. The data also suggest that this increased risk continues into early childhood. No disaggregated data by birthweight were located for measles or malaria, but in the Gambia, where malaria is the main cause of childhood mortality, deaths from malaria are not greater among hungry season births (the season with a high prevalence of LBW births). This suggests that LBW infants are not more susceptible than ABW infants to malaria (18).

Risk of Hospital Admission

During the first 2 years of life, low birthweight is associated with an increased risk of hospital admission for infection. This has been shown for diarrhea and dehydration (19–22), and pneumonia (20,22,23). For diarrhea, the risk may extend beyond 2 years (24). In southern Brazil, after controlling for family income, IUGR children were at almost twice the risk of being admitted to the hospital for diarrhea as ABW infants, but preterm children experienced only a slightly increased risk. In contrast, for pneumonia, both IUGR and preterm children had similar increased risks (22). In northeast Brazil, after controlling for confounding variables, LBW term infants had a fourfold
<table>
<thead>
<tr>
<th>Country (reference)</th>
<th>Design</th>
<th>Gestation</th>
<th>Age (months)</th>
<th>Sample size (deaths)</th>
<th>Birthweight (g)</th>
<th>Risk ratio (95% CI)</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Brazil (4)</td>
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<td>Term</td>
<td>0–6</td>
<td>393 (12)</td>
<td>3,000–3,499</td>
<td>1.0</td>
<td>All causes</td>
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<td>1,500–2,499</td>
<td>10.2 (2.2–46.7)</td>
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<td>6.6* (1.4–31.2)</td>
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<td>Cohort</td>
<td>Term</td>
<td>0–11</td>
<td>4,590 (213)</td>
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<td>All causes</td>
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<td>&lt;2,500</td>
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<td>&lt;2,500</td>
<td>1.7</td>
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<td>Term</td>
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<td>1.0</td>
<td>All causes</td>
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<td>&lt;2,500</td>
<td>1.7</td>
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<td>Cohort</td>
<td>Term + preterm</td>
<td>0–11</td>
<td>687 (83)</td>
<td>≥2,500</td>
<td>1.0</td>
<td>All causes</td>
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<td>&lt;2,500</td>
<td>3.4</td>
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<td>Cohort</td>
<td>Term + preterm</td>
<td>0–11</td>
<td>4,334 (133)</td>
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<td>1.0</td>
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<td>≤2,500</td>
<td>5.8</td>
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<td>Term + preterm</td>
<td>0–11</td>
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<td>1.0</td>
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<td>&lt;2,500</td>
<td>11.0 (8.7–14.4)</td>
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<td>6.7 (3.0–14.9)</td>
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<td>2.5 (0.9–6.7)</td>
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<td>2.9 (1.0–8.3)</td>
<td>Other infections</td>
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<td>3.3</td>
<td>All causes</td>
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<td>Case-control</td>
<td>Term + preterm</td>
<td>0.25–11</td>
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<td></td>
<td>≥2,500</td>
<td>1.9* (1.1–3.6)†</td>
<td>ARI</td>
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<td>1,500–2,499</td>
<td>2.0* (1.1–3.6)†</td>
<td>Diarrhea</td>
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<td>5.0* (1.3–18.6)†</td>
<td>Other infections</td>
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<td></td>
<td>2.3* (1.6–3.4)†</td>
<td>All infections</td>
</tr>
<tr>
<td>India (14)</td>
<td>Cohort</td>
<td>Term + preterm</td>
<td>0–11</td>
<td>659 (19)</td>
<td>&gt;2,500</td>
<td>1.0</td>
<td>ARI</td>
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<td></td>
<td>≤2,500</td>
<td>8.0</td>
<td></td>
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<td>United Kingdom (15)</td>
<td>Cohort</td>
<td>Term + preterm</td>
<td>1–50</td>
<td>5,522 (40)</td>
<td>&gt;2,500</td>
<td>1.0</td>
<td>Bronchitis + pneumonia</td>
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<td></td>
<td></td>
<td>&lt;2,500</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>United States (16)</td>
<td>Cohort</td>
<td>Term + preterm</td>
<td>1–11</td>
<td>51,931 (371)</td>
<td>≥2,500</td>
<td>1.0</td>
<td>Infectious disease</td>
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<td>1,500–2,499</td>
<td>2.4 (1.4–4.0)</td>
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<td>2.5 (1.3–4.5)</td>
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<td>Cohort</td>
<td>Term + preterm</td>
<td>1–11</td>
<td>193,733 (93)</td>
<td>≥2,500</td>
<td>1.0</td>
<td>Diarrhea</td>
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<td></td>
<td></td>
<td></td>
<td>&lt;2,500</td>
<td>7.1</td>
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</table>

*Adjusted for confounders; †90% confidence intervals.
Cl, confidence interval; ARI, Acute respiratory infections.
higher rate of hospital admission in the first 6 months than ABW infants (4). The 
main causes were diarrhea and respiratory infections. In Norway, SGA infants had 
twice the risk of hospital admission for respiratory infections as ABW infants, al-
though the prevalence of respiratory infections was similar in both groups (25). This 
suggests that when SGA infants become infected, their illness may be more severe 
than in ABW infants.

Risk of Morbidity

Table 2 shows the association between birth weight and morbidity (4,14,15,26–31). 
Three studies report diarrhea morbidity, of which two controlled for socioeconomic 
and maternal confounders (4,29). In these two studies, from northeast Brazil and 
Papua New Guinea, LBW infants experienced significantly more days with diar-
rhea (33% and 60%) than ABW infants. An increased risk of diarrhea morbidity 
among LBW infants has also been reported from Guatemala (8) and India (32), but 
the data do not permit calculation of relative risk. Seven studies have reported mor-
bidity for respiratory infections, but only two are adjusted for confounding factors 
(4,30). For one of these, no association was found between LBW and the preva-
ience of cough, or cough with fever (4). In the other, also from northeast Brazil, 
only infants weighing less than 2,000 g were at significant risk of pneumonia (30). 
No studies were located of birthweight and risk of malaria infection, and only one 
of measles morbidity. LBW infants were no more likely than ABW infants to con-
tract measles (15).

Low birthweight infants may be disadvantaged in more ways than just their birth-
weight. For example, in our study of term LBW and ABW infants in northeast Brazil, 
where only low income families were recruited, the LBW group still had poorer 
household environments, fewer resources, and mothers with less education than the 
ABW controls (4). Therefore, potential exists for bias in studies that fail to take pos-
sible confounders into account. Bearing in mind such limitations in most studies, 
nevertheless there is strong evidence from Tables 1 and 2 of a significantly increased 
susceptibility to diarrhea, at least in term LBW infants, and of pneumonia in infants 
weighing less than 2,000 g. There is also strong evidence of an increased risk of hos-
pital admission and death from diarrhea and pneumonia, which may reflect increased 
susceptibility to attack and/or increased severity or duration of infection episodes. 
There is some indirect evidence of an increased risk of death from measles, but a de-
creased susceptibility to malaria.

DIFFERENTIAL SUSCEPTIBILITY TO INFECTION

Among term IUGR infants in Guatemala, diarrheal rates in the first 2 months of life 
were negatively associated with ponderal index (33). Because a higher ponderal in-
dex in IUGR infers a symmetric (stunted) infant, these data can be interpreted as in-
dicating a higher risk in stunted than in wasted LBW infants. In Norway, the risk of 
hospital admission during infancy in symmetric (stunted) SGA term infants was
<table>
<thead>
<tr>
<th>Country</th>
<th>Design</th>
<th>Gestation</th>
<th>Age (months)</th>
<th>Sample size</th>
<th>Birthweight (g)</th>
<th>Risk ratio (95% CI)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethiopia (26)</td>
<td>Cohort</td>
<td>Term</td>
<td>3–40</td>
<td>201</td>
<td>≥2,500</td>
<td>1.0</td>
<td>All infections</td>
</tr>
<tr>
<td>Brazil (4)</td>
<td>Cohort</td>
<td>Term</td>
<td>0–6</td>
<td>393</td>
<td>3,000–3,499</td>
<td>1.5 (1.1–2.1)</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>India (27)</td>
<td>Cohort</td>
<td>Term</td>
<td>0–3</td>
<td>152</td>
<td>≥2,500</td>
<td>1.0</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Guinea (28)</td>
<td>Cohort</td>
<td>Term + preterm</td>
<td>2 days–3 months</td>
<td>267</td>
<td>≥2,500</td>
<td>1.0</td>
<td>Mostly sepsis and ALRI</td>
</tr>
<tr>
<td>Papua New Guinea (29)</td>
<td>Cohort</td>
<td>Term + preterm</td>
<td>0–17 18–35 36–59</td>
<td>400</td>
<td>&lt;2,500</td>
<td>1.7 *(1.4–2.1)</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Brazil (30)</td>
<td>Case-control</td>
<td>Term + preterm</td>
<td>0–23</td>
<td>1,300</td>
<td>≥2,500</td>
<td>1.4</td>
<td>Pneumonia</td>
</tr>
<tr>
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<td>Cohort</td>
<td>Term + preterm</td>
<td>0–11</td>
<td>659</td>
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<td>1.0</td>
<td>ARI</td>
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<tr>
<td>Uruguay (31)</td>
<td>Cohort</td>
<td>Term + preterm</td>
<td>0–35</td>
<td>166</td>
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<td>1.0</td>
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</tr>
<tr>
<td>United Kingdom (15)</td>
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<td>Term + preterm</td>
<td>0–23</td>
<td>690</td>
<td>≥2,500</td>
<td>1.0</td>
<td>ALRI</td>
</tr>
</tbody>
</table>

*Adjusted for confounders.
ARI, acute respiratory tract infection; CI, confidence interval; ALRI, acute lower respiratory tract infection.
twice that of ABW infants (odds ratio 2.0, 95% confidence interval 1.2-3.3), but no such risk was evident for asymmetric (wasted) infants (25). When the symmetric babies were further disaggregated, the increased risk was confined to the infants whose mothers smoked daily in early gestation. The major cause of hospital admission was for respiratory infections. Whether the increased risk is caused by the effect of periconceptional smoking on fetal immune function or to postnatal exposure to passive smoking, is not made clear.

LOW BIRTHWEIGHT AND INFECTION IN ADULTHOOD

Novel findings from the Gambia indicate that hungry season births have a tenfold greater risk of premature death in young adulthood than infants born in other months, with a predominance of infectious deaths (40%) and maternal deaths (15%) (34). A permanent reprogramming of the immune system during fetal life as a result of nutritional stresses is considered a likely cause, and particular emphasis is given to the vulnerability of the thymus to damage, owing to its complex structure, diverse cellular content, and its specialized function in thymopoiesis (18,34,35).

MECHANISMS FOR INCREASED SUSCEPTIBILITY TO INFECTION

Fetal and Postnatal Programming

The concept of programming, in which a stimulus applied at a sensitive period of development has lifelong effects, is now well established (36). As several components of the immune system mature during fetal life (37), with functional lymphocytes appearing by 10 to 12 weeks’ gestation, this system is vulnerable to maternal undernutrition and to possible reprogramming (2,18), and animal studies clearly show a sustained effect of fetal undernutrition on immune function (38,39), even lasting into the F2 and F3 generations (40).

In late gestation, a rapid increase occurs in fetal plasma cortisol levels with an associated switching of the cell cycle from proliferation to differentiation (41). This stimulus to maturation is thought to reset the hypothalamic-pituitary-adrenal (HPA) axis in order to prepare the fetus for extrauterine life. In maternal undernutrition and other conditions associated with fetal growth retardation, the fetal HPA axis is activated earlier and fetal cortisol levels remain raised for a longer period before delivery (41). This reduces the period available for cell proliferation and may reduce cell number permanently. Raised plasma cortisol is known to be associated with thymic atrophy (42), and in animal experiments, maternal zinc deficiency is also associated with raised cortisol levels (42). This may be one mechanism whereby maternal undernutrition permanently impairs immune function.

Prentice et al. (18) point to toxic exposure as a further possibility for fetal nutritional programming of immunity. For example, transplacental transfer of aflatoxin occurs in proportion to maternal exposure, and aflatoxin is a potent immunosuppressant.
Micronutrient Deficiencies

Not only may immune function be adversely affected in utero as a result of maternal undernutrition or toxic exposure, but once born, LBW infants are at increased risk of nutrient deficiencies. For example, preterm infants are born with much less zinc, copper, and iron than term babies because approximately 50% of the transfer from mother to fetus occurs in the last 6 to 8 weeks of gestation (43). Fetal liver retinol stores double between 25 and 37 weeks' gestation (44), and low plasma retinol has been reported in preterm infants at delivery (45). Preterm infants seem to be particularly susceptible to postnatal depletion of liver vitamin A reserves, with a 50% reduction in mean hepatic concentration in the first 2 months of life, in contrast to term infants who show no reduction (46).

Also, less zinc, copper, iron, and vitamin A are found in IUGR term babies than in ABW infants because their liver size is 30% to 40% smaller (47). About half the newborn’s body copper content is in the liver, and a quarter of the zinc. Term neonates with small livers also have lower hepatic concentrations of copper and zinc than larger babies (48,49). As micronutrients play a pivotal role in immune function (38,39), these differences in micronutrient reserves are likely to affect preterm infants adversely in the short term and IUGR infants in the long term. Preterm neonates supplemented with zinc recovered their cell-mediated immunity more quickly than controls (39). In term LBW infants, zinc supplementation for 8 weeks was associated with a 28% reduction in diarrhea prevalence in the first 6 months of life, but no significant reduction in the prevalence of respiratory infections (50).

Reduced Breast-Feeding

A lower prevalence of breast-feeding is often reported for LBW infants compared with ABW infants, and this can be expected to increase their risk of infection, particularly to sepsis, diarrheal diseases, and otitis media. In our morbidity studies in northeast Brazil, the median durations of breast-feeding in LBW and ABW infants were 2.8 and 3.4 months, respectively. Although in the sample as a whole, feeding mode was strongly related to the rate of onset of diarrhea, inclusion of feeding mode in the multiple regression analyses had no impact on the estimated effects of birthweight on morbidity outcomes (4).

THE IMMUNE SYSTEM

This complex and vital defense system is described in detail elsewhere in this volume. In summary, the two principal response types are (a) adaptive or antigen-specific mechanisms, of which the two main components are the immunoglobulin-antibody system and cell-mediated immunity; and (b) innate or nonspecific responses, which include the complement system, phagocytes, lysozyme, interferon and other humoral factors, and the physical barriers of skin and mucous membranes.
Development of the immune system begins around the sixth week of gestation, and responses to mitogens and natural killer cell activity are detectable by 10 weeks. Maturation occurs predominantly in utero (51). When the intrauterine environment is disturbed, as in IUGR or preterm births, cell-mediated immunity is the main component affected.

**Specific Immunity**

**Immunoglobulins**

Little immunoglobulin G (IgG) is transferred from mother to fetus before 32 weeks' gestation and babies delivering before this time have very low serum IgG concentrations, which decline further during the first weeks of life. Hypoimmunoglobulinemia is thought to contribute to the high frequency of sepsis (52,53) and respiratory and meningeal infections in preterm LBW neonates (54). Giving intravenous immune globulin to neonates with sepsis improves their survival sixfold, and when given prophylactically has a small but demonstrable benefit in reducing the incidence of infection (52,55).

Term SGA neonates have lower serum concentrations of IgG than ABW neonates, and this has been ascribed to smaller placental surface area in the former, which limits fetal transfer (32,56). IgM concentrations in SGA neonates did not differ from ABW infants in these studies, but conflicting findings were reported for IgA. Neither IgA nor IgM is acquired transplacentally.

**Antibodies**

Active neutralizing antibody responses in IUGR infants following vaccination to bacille Calmette–Guerin vaccine (57), hepatitis B (58), and polio virus vaccines (59) are reported to be similar to the responses in ABW infants.

**Cell-mediated Immunity**

The lymphoid tissues (thymus, spleen, and lymph nodes) of the fetus are more severely affected by maternal undernutrition than other tissues and organs (39). These are the key sites for the production and processing of T lymphocytes, and hence for mounting cell-mediated responses to infection. Term SGA and preterm LBW newborns have fewer T lymphocytes than ABW infants (32,39,60), but by 3 months preterm infants have normal levels, whereas SGA infants continue to have reduced numbers for several months or even years (39,61). Within the T-cell subpopulation, the helper CD4+ cells are reduced in number, and the CD4+:CD8+ helper:suppressor ratio is significantly lower in term SGA than in ABW infants (56).

Reduced lymphocyte stimulation response to phytohemagglutinin (PHA) at birth has been reported in both preterm and term SGA neonates, the extent of the reduc-
tion paralleling the reduction in T-lymphocyte count (61). This reduction persists only in SGA infants and is associated with lower serum thymic hormone activity. Moscatelli et al. (62) found normal responses to PHA in most term SGA infants at birth, and the remainder normalized by 3 weeks. In Brazil, term LBW infants tested at 6 months had normal responses to PHA (50).

**Nonspecific Immunity**

**Complement**

Cord blood C3 levels are significantly lower in preterm and term SGA neonates compared with ABW term newborns (32,56). As placental transfer occurs in the last trimester, and fetal C3 synthesis occurs predominantly in the liver, it is plausible for both preterm and IUGR newborns to be adversely affected, but by different routes. By 6 months, serum C3 concentrations are similar (32).

**Polymorphonuclear Leukocytes**

Phagocytosis, intracellular bacterial killing capacity, and chemotaxis of polymorphonuclear leukocytes are deficient in preterm newborns. By 2 weeks of age, phagocytosis becomes normal, and this can be achieved in 5 days by giving vitamin E (63), but other functions remain deficient.

**FUTURE RESEARCH**

Methodologically robust studies with sufficient sample size are needed to clarify whether term LBW infants have an increased risk of respiratory infections. As preterm infants weighing less than 2,000 g have impaired lung function until at least 7 years of age, future incidence studies should have sufficient sample size to allow disaggregation of preterm and term LBW infants.

Comparative studies of the susceptibility of LBW and ABW infants to malaria, measles, and the human immunodeficiency virus are warranted. These studies should include sensitive measures of immune function.

Little is known about infection rates and immune function in LBW term infants who differ in their body proportions at birth (stunted vs wasted). This is an area that could provide useful insights into the functional consequences of sensitive periods of development.

Given the significance to public health of the likely association between birthweight and infection in adulthood, the long-term consequences of LBW should be a priority area for further research.

Further nutritional interventions, in which both morbidity and immune function are outcomes, could help elucidate important causal factors for increased susceptibility to infection and guide effective public health strategies.

Acknowledgment: I thank Melissa Dan for contributing to this review.
REFERENCES


132 LOW BIRTHWEIGHT INFANTS, INFECTION, AND IMMUNITY


**DISCUSSION**

*Dr. Wasantwisut:* I found the Brazil zinc supplementation trial very interesting. What was the iron and vitamin A status of these infants? You mentioned before that these low birthweight infants are susceptible to other deficiencies besides zinc. Secondly, could you comment on the failure to restore serum zinc to normal after zinc supplementation? I think other studies have found the same thing. Could this be caused by infection or an inflammatory response? In populations where inflammation is widespread, it is very difficult to bring the serum zinc back into the normal range.

*Dr. Ashworth:* One of the discussions that we had in designing the study was whether we should give a cocktail of all three nutrients. In the end we decided just to go with zinc. There is good reason to believe that the vitamin A and iron status would not be particularly good, for the same reasons as for zinc. However, I cannot say what the actual status was; we just focused on zinc. In relation to infection and its effect on serum zinc, the analyses of serum zinc and thymulin were very kindly done by Dr. Chandra. The question of infection was raised by him when the serum zinc values came out low. We, therefore, looked particularly at the infection status before the blood was taken, but were unable to explain the low values on that basis.

*Dr. Suskind:* In your review of the literature on the low birthweight infant, did you ever come across any studies which looked at supplementing low birthweight infants with more than just zinc? Based on our experience with children who have malnutrition after birth, we found in Thailand, as others have found, that the requirement for catch-up may be as high as 150% of the recommended daily allowance in energy, i.e., 180 kcal/kg protein at 4 g/kg, and 150% of the RDA for vitamins and minerals. I wonder if anyone has ever intervened in low birthweight children with that sort of regimen, looking not only at growth but also at immune status.

*Dr. Ashworth:* I am not aware of any community-based study. I would be very interested in that, too.

*Dr. Marini:* It is very important to measure the length of the baby in intrauterine growth retardation. Having measured the length of the baby, the ponderal index can be calculated and the category of growth retardation defined. The likelihood of growth recovery is strongly re-
lated to the ponderal index. My second comment is about the distinction you made between industrialized countries and developing countries. In fact, similar babies are to be found even in the industrialized countries. I am referring particularly to babies who receive betamethasone in utero to enhance pulmonary maturation. These babies have depressed immune function and often die of sepsis.

**Dr. Ashworth:** We weighed the children and measured their length at birth, 4, 8, 12, 17, and 26 weeks and at one year. You are quite right that if you classify the children by ponderal index and length for age, those children in the Brazilian setting with a low ponderal index had very rapid growth in the first 8 weeks, and then they maintained that Z-score, before drifting down a little. Although the stunted ones start off at exactly the same standard deviation score in terms of weight for age, they diverge completely from the wasted ones. They improve in their Z-score only a little, and from about 8 weeks they maintain their Z-score in parallel with the wasted group but on a lower track (1). It is certainly very important to characterize these children in terms of their length for age at birth, their ponderal index, and their gestational age.

**Dr. Woodward:** Has anybody produced any measurements of endotoxin in the blood of low birthweight infants in the way that Dr. Suskind was suggesting this morning with regard to postweaning malnutrition?

**Dr. Ashworth:** I am not aware of any.

**Dr. Marini:** There are data on endotoxin levels in very low birthweight infants without bacteremia (2), which was considered to be one of the causes of necrotizing enterocolitis.

**Dr. Woodward:** The reason I asked the question was that I would have thought it might at least provide the beginnings of an understanding of a low serum zinc measurement.

**Dr. Coovadia:** We did a study some years ago on anti-endotoxin antibodies. It was a randomized, controlled trial on newborn babies to check their endotoxin levels (3). The aim was to use antibody against endotoxins. Not surprisingly, many of these babies had endotoxin but were culture negative. Our results showed that anti-endotoxin antibodies had no effect whatsoever.

**Dr. Tantibhedhayangkul:** There is an interaction between zinc and copper, and even between zinc and iron. We gave zinc to malnourished children at a dose of 1 mg/kg bodyweight and found a fall in serum copper together with a fall in ceruloplasmin. Do you know what happened to the other micronutrients in your study?

**Dr. Ashworth:** These interactions are very important, and we were aware of them when we were starting the study. I think that this level of dosage (5 mg/d for 8 weeks) was probably not sufficient to interact adversely with iron. We did not measure serum copper.

**Dr. Wakelin:** A theory to explain the present increase in atopy and asthma in developed countries is reduced exposure to infectious organisms in early life. Your review shows that low birthweight infants have an increased exposure, or at least an increased susceptibility to infections. Pathogens are not passive agents. Many of them can polarize or program the immune response in one direction or another. Have you any views on the long-term consequences of such an increased exposure to infection in low birthweight infants in later life, other than mortality?

**Dr. Ashworth:** I cannot answer that. It is outside my area of expertise. Maybe someone else can comment?

**Dr. Calder:** Some data may be relevant to that question. A study from Southampton, United Kingdom (4) found a positive correlation in cases where head circumference at birth was related to circulating IgE in adulthood; in other words, the larger the head, the higher the circulating IgE at approximately 60 years of age. I think the odds ratio of having elevated serum IgE in adulthood was about 4.5 in the group with the largest head circumference at birth. A second study (5) was a related one, where birthweight was related to the occurrence of allergy, asthma,
Dr. Chandra: In relation to autoimmune diseases and low birthweight, there are no prospective studies that I know of. However, in looking at patients with rheumatoid arthritis and control them for other variables, they are more likely to have been of low birthweight. Thus there may be an increased risk of autoimmune disease, especially rheumatoid arthritis, in low birthweight individuals. My second point is about low birthweight and atopy. Some evidence indicates that the incidence of atopy varies in low birthweight infants, depending on whether the infant is preterm or small for gestation, and whether or not there is a family history. Some studies indicate that given a positive family history, preterm babies have nearly a 30% to 35% higher risk of eczema at about 3 to 5 years of age, whereas this is less true for small gestational age infants. So, some interaction may exist between rates of infection, family history, and the incidence of atopic disease.

Dr. Marini: I would like to stress that allergy is not only the consequence of a preterm birth, but could be the cause as well. Several studies (6) show an increased likelihood of an allergic history in mothers delivering preterm babies. This is probably related to increased prostaglandin production or altered cytokine production during intercurrent infectious disease. Thus, allergy can be viewed as both a cause of and a consequence of preterm birth.

Dr. Wakelin: As this workshop is concerned with the interaction between nutrition, infection, and immunity, the point I wanted to emphasize was that several studies now show that nutritional disturbances can have immunologic consequences. These may be related to specific activities of the pathogen. Dr. Woodward showed how mice infected with a parasite had a polarized cytokine response. That was presumably a consequence of nutrition affecting immunity to the pathogen and influencing the immune response. I think this might be an important factor to bear in mind when looking at population studies, particularly where the population is exposed to a lot of infectious disease.

Dr. Keusch: Pursuing the issue of the relation with low birthweight and the outcomes you described, Leonardo Mata, of the Institute of Nutrition of Central America and Panama (INCAP) in Guatemala, used to talk about maternal care in a generalized sense as maternal technology—that is, the understanding of what you need to do to keep young infants growing and healthy. This is learned and not innate; it is learned in part by lessons from other women who have had babies, and it is learned in the course of having multiple babies. I suspect that most low birthweight babies in your study were firstborns, but I wonder about your adequate weight babies—whether those were subsequent children and whether some of the explanation for differences may lie in the maternal technology component of taking care of young infants.

Dr. Ashworth: There was no significant difference in parity (7). In relation to your question about maternal care, we did collect a lot of information about the environment and the maternal histories. Although some of these variables can be controlled for in the regression analysis, the subtle aspects of maternal care are difficult to measure and control for, so I think that is an important point you raised.

Dr. Cochran: Could you clarify the effects you were seeing? Do you think they were purely related to the nutritional insult that the children suffered in utero, or were those same children still having nutritional deficiencies throughout the study period?

Dr. Ashworth: It is very difficult to answer that without doing a randomized, controlled trial. I think that fetal undernutrition might be having an effect on immune function through programming, but even if that was not the case, there could be differences in micronutrient reserves because of their much smaller liver size. We did look at diet between the two groups from 0 to 6 months and we did not see any difference between the low birthweight
and the adequate birthweight groups on a cross-sectional basis in terms of the types of food they were eating.

Dr. Suskind: Does the literature show any more extensive characterizations of the immune system in low birthweight infants versus appropriate for gestational age infants other than the cellular immune response?

Dr. Ashworth: Yes, studies have shown an impairment. Dr. Chandra may want to comment on his studies.

Dr. Chandra: We published some data in the mid-1970s. We found no problems with phagocytosis or ingestion of bacteria, but did find a modest reduction in intracellular killing of bacteria. There was also a reduction in complement levels, particularly C3, in the small for gestational as well as preterm babies. We followed the infants for more than one year, and most of the abnormalities disappeared within 3 to 6 months, in contrast to cell-mediated immunity, which continued to show some depression in most infants. This prolonged even intergenerational effect has also been shown in controlled animal experiments.

Dr. Farthing: Have you considered any controlled interventions during pregnancy? At what point in pregnancy do you think you would have to intervene?

Dr. Ashworth: In terms of preventing low birthweight, several possible interventions exist (8). Improving maternal nutrition with micronutrient or balanced protein and energy supplementation are two possibilities; others are malaria prophylaxis and not smoking. I think those are probably the top four.

Dr. Farthing: Have any of these been formally tested in the population that you were studying?

Dr. Ashworth: Not in that part of Brazil, but randomized, controlled trials on prevention of low birthweight have been done in other countries.

Dr. Tontisirin: With a colleague, I recently prepared a paper about a community-based program to reduce low birthweight. The key thing is to obtain the cooperation of pregnant women and persuade them to attend for antenatal care. We propose to create a social mobilization mechanism to link with the antenatal care services and increase coverage from 35% or 50% to more than 85%. Second, we aim for at least four or five antenatal care visits. This regimen has been successfully used in Thailand during the last 15 or 20 years. At the antenatal care visits, the woman has a high-risk checkup, health and nutrition education especially relating to food taboos and food beliefs and the importance of an adequate diet. In addition, she receives advice to stop smoking and drinking alcohol. She also gets multivitamin and iron supplements from the start, to be continued throughout pregnancy. We have shown that by these means we can increase birthweight in marginalized populations. For high risk pregnancy, a referral system is required. One other point I would like to make is that several studies in India have shown that low birthweight is associated with severe anemia during the pregnancy.

Dr. Fawzi: We carried out a trial in Tanzania among pregnant women who were human immunodeficiency virus positive. We found that micronutrients, mainly multivitamin supplements, resulted in nearly a 40% reduction in low birthweight, among other improvements in pregnancy outcome (9).

REFERENCES


