Clinical Outcome of Low Birthweight, Long-Term Consequences


Abstract

Infants born with low birthweight (LBW) have poorer neurodevelopmental outcomes compared with their term counterparts with appropriate weight for gestational age. The perinatal period is a time of high energy and high nutrient needs, and any process, such as preterm birth, poor nutrition or placental insufficiency, that interrupts the concentrated flow of nutrients to the fetus may result in babies with LBW. Therefore, it makes logical sense that at least part of the cognitive deficits may be explained by nutritional deprivation. The nutrients commonly deficient in LBW infants include protein and energy and micronutrients such as iron, zinc and long chain polyunsaturated fatty acids. In this review, we aimed to determine the effect of nutrient supplementation on neurodevelopment in LBW infants. While few trials have supported the hypothesis that nutritional supplementation improves neurodevelopment, many studies are limited by sample size and methodological shortcomings. Further large-scale rigorously designed intervention trials, with long-term neurodevelopment follow-up, are required to determine the optimal nutritional supplements and the timing of their administration to LBW infants.

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Improving the Neurodevelopmental Outcomes of Low-Birthweight Infants

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Abstract

Infants born with low birthweight (LBW) have poorer neurodevelopmental outcomes compared with their term counterparts with appropriate weight for gestational age. The perinatal period is a time of high energy and high nutrient needs, and any process, such as preterm birth, poor nutrition or placental insufficiency, that interrupts the concentrated flow of nutrients to the fetus may result in babies with LBW. Therefore, it makes logical sense that at least part of the cognitive deficits may be explained by nutritional deprivation. The nutrients commonly deficient in LBW infants include protein and energy and micronutrients such as iron, zinc and long chain polyunsaturated fatty acids. In this review, we aimed to determine the effect of nutrient supplementation on neurodevelopment in LBW infants. While few trials have supported the hypothesis that nutritional supplementation improves neurodevelopment, many studies are limited by sample size and methodological shortcomings. Further large-scale rigorously designed intervention trials, with long-term neurodevelopment follow-up, are required to determine the optimal nutritional supplements and the timing of their administration to LBW infants.

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The trajectory of growth is greatest during the perinatal period, which is the time that includes late pregnancy and early postnatal life. During the last trimester of pregnancy the normal fetus will grow from approximately 900 to
3,400 g, more than tripling in weight. The newborn term baby will double birthweight in the first 4 months of life and will again nearly double in size over the next 24 months, but will not achieve adult size until late adolescence. The brain, on the other hand, will achieve adult size (approximately 1,200 g) by about 2 years of age. In the last trimester of pregnancy, brain weight will increase from approximately 150 to 400 g, and between term birth and 6 months of age the brain will again double in size, reaching approximately two thirds of adult brain weight [1]. The composition and structure of the brain also changes dramatically during this time [2], and these changes continue well into childhood.

The perinatal period is characterized by high energy and high nutrient requirements necessary to sustain the high growth rates. It is therefore not surprising that any process, such as preterm birth, poor nutrition or placental insufficiency, that interrupts the concentrated flow of nutrients to the fetus will result in babies with low birthweight (LBW). The brain appears particularly sensitive to the nutrient deprivation associated with LBW, as infants who are born with LBW are more likely to have lower scores on neurodevelopmental tasks into childhood compared with term, normal-birthweight infants [3]. Preterm infants are at particular risk for long-term cognitive and educational problems directly proportional to their degree of prematurity, with those most preterm demonstrating a mean intelligence quotient (IQ) of 0.8–1.5 standard deviations (SD) lower than children who were born at term [4]. Recent evidence also suggests there are even higher rates of developmental delay in preterm infants born growth restricted compared with appropriately grown preterm infants [5, 6]. Children born at term and with LBW are twice as likely to have an IQ that is 2 SD lower than term-born appropriately grown infants [7].

Strategies to improve the neurodevelopmental outcome of children born with LBW are important, and many interventions have focused on nutritional approaches applied during the period immediately after birth, especially for preterm infants who are born before the last trimester of pregnancy is complete and the concentrated nutrient supply delivered across the placenta is prematurely ceased. The nutrients that are commonly deficient in LBW infants include protein and energy as well as micronutrients such as iron, zinc and long-chain polyunsaturated fatty acids (LC-PUFA) [2]. The focus of this review, therefore, is to determine the effect of nutrient supplementation on neurodevelopment in LBW infants. The review is limited to randomized controlled trials (RCTs) designed to assess the effects of enteral nutrition interventions during the postnatal period. Other study designs have not been considered because complex neurodevelopmental outcomes are influ-
enced by many factors including sex, perinatal morbidity as well as social and
environmental influences [4], and RCTs remain the gold standard methodology to minimize the biases of these other factors and show cause and effect relationships.

A comprehensive literature search was undertaken to identify systematic re-
views of RCTs or RCTs including postnatal protein-energy, micronutrient or
LC-PUFA supplementation in LBW infants and reported neurodevelopmental
outcomes.

**Protein-Energy Supplementation of Preterm Infants**

The effect of protein-energy enrichment in the postnatal period on neurodevel-
opment of preterm infants has been summarized in five Cochrane Systematic
Reviews [8–12] involving 9 RCTs conducted between mid-1960 to mid-2000
[13–21]. The early trials compared differing concentrations of protein in for-
mula or breast milk while in hospital [13–18], and the more recent trials inves-
tigated the effect of providing protein-energy-enriched formula or breast milk
after discharge [19–21].

*In-Hospital Supplementation of Formula Compared with Donor
Human Milk*

In a systematic review of formula versus donor human milk (either as the sole
diet or as a supplement to mother’s own milk) only one trial was included [9].
This seminal study conducted by Lucas et al. [15, 22, 23] in the 1980s compared
preterm formula (2 g protein and 80 kcal/dl; 2.5 g protein/100 kcal) with donor
breast milk (1.07 g protein and 46 kcal/dl; 2.3 g protein/100 kcal). In this paral-
lel RCT, women who chose not to breastfeed were randomized to preterm for-
mula or donor breast milk as the sole diet (trial 1), and women who chose to
breastfeed were randomized to receive preterm formula or donor breast milk as
a supplement to breast milk (trial 2) [15]. At 9 months of age, on combining tri-
als 1 and 2, a significant benefit was found in developmental quotients (DQ)
with the preterm formula (preterm formula 100.4, SD 10.7, versus banked donor
human milk 97.9, SD 9.6; 95% CI: 0.4–4.6) [23]. At 18 months’ corrected age, no
benefit to mental development was found in either trial 1 or trial 2 or on meta-
analysis of both trials (n = 387, weighted mean difference, WMD, 1.24, 95%
CI: −2.62 to 5.09) [9].
In-Hospital Supplementation with Protein and Energy Using Human Milk Fortifiers

While human milk is the preferred base feed for preterm infants because of its immunological properties, it is well recognized that protein, energy and micro-nutrient supplementation is needed to achieve appropriate growth rates. However, in a systematic review of multicomponent fortification of human milk versus no fortification, there was only one trial that assessed neurodevelopment [10]. In this trial, 275 infants born weighing <1,850 g whose mothers chose to breastfeed were randomized to receive 0.7 g protein and 14 kcal added to 100 ml of breast milk or no additional protein-energy supplement [18]. Neurodevelopment was assessed at 18 months’ corrected age with no significant difference found (MD 2.2, 95% CI: −3.35 to 7.75) [10].

In-Hospital Supplementation with Protein and Energy Using Infant Formulas

Lucas et al. [16] in another well-known study compared term formula vs. preterm formula in preterm infants. This study included two parallel trials in which infants born weighing <1,850 g were randomly allocated to receive a protein-energy-enriched formula containing 2.0 g protein and 80 kcal/dl (2.5 g protein/100 kcal) or standard formula of 1.45 g protein and 68 kcal/dl (2.1 g protein/100 kcal) [16]. The first trial (trial A) included infants who were not receiving any breast milk, so the test formulas were the sole diets, and the second trial (trial B) included infants who were receiving some breast milk so that the test diets were a supplement to mother’s milk. In trial A, psychomotor development, but not mental development, at 18 months’ corrected age was higher with protein energy enrichment (mean difference, MD, 14.7, 95% CI: 8.7–20.7) [16]. There were no neurodevelopmental differences found in trial B. When trials A and B were combined at 18 months, there were no differences found in mental development, but the improvement in psychomotor development remained (MD 6.2, 95% CI: 2.4–10.0) [16], and there was a significant sex by diet interaction such that boys fed the protein-energy-enriched formula had an 8-point gain in mental development (95% CI: 2–13) [16].

When the same cohort was assessed at 7.5–8 years of age (84% follow-up rate) no differences in any IQ measures were found in either trial A or trial B or when trials A and B were combined [24]. However, the verbal IQ of children who were fed the protein-enriched formula in trial A was higher compared with control but did not reach statistical significance (MD 4.8, 95% CI: −0.6 to 10.02) [24]. Al-
though no sex by diet interaction was reported, post hoc analyses indicated that boys in trial A who had protein-energy-enriched formula as the sole diet had a 12.2 increase in verbal IQ (95% CI: 3.7–20.6) compared to boys who had standard formula [24]. We have excluded from this review results for a subset (n = 95) of the children assessed as neurologically normal at 7.5–8 years of age and who were assessed again at 16 years of age. This highly selected population now constitutes an exploratory analysis with a high risk of bias [25]. Although the neurodevelopmental data are not strong with trial A including the smallest numbers and extensive exploratory analyses, nutrient-enriched preterm formulas are now common practice for all preterm infants who require formula complements.

Nevertheless, there is significant interest in further enriching protein concentration based on growth and other metabolic studies. A systematic review of the effects of higher versus lower protein intakes in exclusively formula-fed infants included three trials reporting developmental outcome [8]. These trials, beginning early in the postnatal period in LBW infants, have yielded mixed results on neurodevelopmental outcomes [8]. The earliest and largest trial included in the review was conducted in the 1960s and included infants <2,000 g (n = 304) [13]. This study reported no difference in overall IQ at 3 and 5–7 years of age between infants fed very high protein content formula (5 g protein/100 kcal providing 6.0–7.2 g/kg per day) compared with lower protein content formula (2.5 g protein/100 kcal, providing 3.0–3.6 g/kg per day). However, in infants with birthweights <1,300 g, the infants fed the higher protein formula had a significantly increased incidence of IQ <90 at 3 (RR 0.30, 95% CI: 0.14–0.64) and 5–7 years of age (RR 0.31, 95% CI: 0.15–0.66) when compared to infants fed lower protein formula [8]. The formula was isocaloric; however, the very high protein formula had 17% more minerals. Results of this early study have led to a cautious approach to increasing protein concentration and the recommendation from the Cochrane Systematic Review that protein intakes greater than 4 g/kg per day should be considered experimental [8].

The two remaining trials included in the review were limited primarily by small sample sizes and by either inadequate description of trial details/procedures or large loss to follow-up. One trial (n = 48), fed very LBW preterm infants isocaloric formula of 3.0 g protein/100 kcal to provide 3.2 g/kg per day protein compared with 2.3 g/100 kcal providing 2.6 g/kg per day from 3 weeks of age [14]. No difference in neurodevelopmental assessments (tests not specified) were reported at 6 months, 1 or 2 years of age [8]. The remaining trial (n = 26) fed isocaloric formula yielding 2.6 g/kg per day (2.2 g protein/100 kcal) of protein compared with 3.1 and 3.8 g/kg per day (2.7 and 3.2 g/100 kcal) of protein to very LBW infants [17]. Infants receiving the higher protein performed significantly better on orientation (p = 0.0003), habituation (p = 0.003) and auto-
nomic stability (p = 0.01) clusters of the Neonatal Behavior Assessment Scale when assessed at approximately 36–37 weeks’ postmenstrual age [8].

Postdischarge Supplementation with Protein and Energy for Breast Milk and Formula

As almost all of the in-hospital studies did not continue supplementation beyond discharge, it is possible that the intervention period was too short to ‘catch up’ the nutrient deprivation associated with prematurity and hence see consistent neurodevelopmental advantages. With this rationale, postdischarge protein and energy supplementation has been investigated for preterm infants. The key trials are summarized in two systematic reviews, one comparing term formula versus preterm formula [11] and one comparing fortified with unfortified human milk [12]. Only two trials of preterm versus term formula have assessed neurodevelopment at 18 months’ corrected age [11]. The trials included preterm infants with birthweight <1,750 g. In one trial, only infants who were growing normally with a rate of weight gain ≥25 g/day at time of discharge were eligible to participate [19]; in the other trial, infants had to weigh <3,000 g at time of discharge [20]. Infants were randomized to receive nutrient-enriched formula (72–80 kcal and 1.85–2.2 g protein/dl) or standard term formula from discharge to 6 [19] or 9 [20] months after term. A meta-analysis of data from both trials (n = 299) showed no significant difference in mental (WMD 0.23, 95% CI: –2.99 to 3.45) or psychomotor development (WMD 0.55, 95% CI: –1.95 to 3.05) [11]. Only one small trial (with a high loss to follow-up) of postdischarge fortification of human milk was found for inclusion in a systematic review [12]. Thirty-nine preterm infants born at <33 weeks’ gestation, with birthweight 750–1,800 g were included in the trial [26]. Infants were randomized to have half of the daily breast milk intake fortified to achieve an approximate protein and energy content of 2.2 g and 81 kcal/100 ml or no fortification (1.3 g protein and 68 kcal/100 ml) for 12 weeks. No significant difference in developmental outcome was found at 18 months’ corrected age [intervention mental development index (MDI) 100 (1st to 3rd centile; 72–102.5) versus control 91 (1st to 3rd centile; 77–107)] [12].

Protein-Energy Supplementation of Term Growth-Restricted Infants

Limited data exist for term-born infants who are born small for gestational age (SGA). The benefits of a nutrient-enriched formula compared with standard formula for SGA term infants (>37 weeks and birthweight <10th percentile for
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sex/age) also require more clarification. At 9 months of age, infants fed the nutrient-enriched formula from week 1 after birth until 9 months of age, had a significant disadvantage (MD −2.5, 95% CI: −4.6 to 0.4) in overall DQ as assessed with the Knobloch Developmental Screening Inventory. There was a significant sex by treatment interaction with girls fed the nutrient-enriched formula performing significantly poorer (MD −5.1, 95% CI: −7.8 to −2.4) compared to boys (MD 0.9, 95% CI: −2.4, 4.2). At 18 months, however, the same cohort of infants assessed using the Bayley Scales of Infant Development (BSID) showed that the enriched formula had no significant effect on mental or psychomotor development compared with standard formula [27].

Although protein-energy supplementation for LBW infants has been widely studied, there are surprisingly few well-conducted trials with neurodevelopmental outcomes that have adequate sample sizes to draw robust conclusions regarding the direct effect of protein-energy supplementation on cognitive and psychomotor outcomes.

### Micronutrient Supplementation

Individual micronutrient building blocks, which do not contribute energy, are also considered important for brain development, and a number of studies have specifically investigated individual nutrient supplementation for LBW infants, although LC-PUFA have been the most widely studied in relation to neurodevelopment.

#### Zinc and Iron

Zinc supplementation and neurodevelopment has been investigated in two trials of LBW term infants in low-income families in Brazil and India [28, 29]. In one trial in an impoverished community in India, 1,250 infants were randomized to receive a daily supplement of: (1) 5 mg of zinc sulfate, in a micronutrient mix of riboflavin, calcium, phosphorus, folate and iron supplement, or (2) the same micronutrient mix without zinc, or (3) 5 mg of zinc sulfate with riboflavin or (4) riboflavin only [29]. Treatment was given from 30 days of age to 9 months. 200 infants were randomly selected from groups 1 and 2 for neurodevelopmental assessment at 6 and 10 months of age. No significant difference in mental development was found at either time point (MDI intervention 83, SD 9 vs. control 82, SD 9; intervention 86, SD 5 vs. control 86, SD 5, at 6 and 10 months, respectively) [29].
In the only other trial of zinc supplementation where neurodevelopment was measured, the intent was to randomize 250 infants to receive a 5-mg oral solution of zinc compared with no supplementation from birth to 8 weeks of age [28]. There was an error in the manufacture of the solution such that it only contained 1 mg of zinc rather than 5 mg. At this stage, 134 infants had been randomized. The study continued with a further 71 infants enrolled to receive 5 mg of zinc, i.e. not randomized, to give a total sample size of 134. No significant difference in either mental or psychomotor development was found at 6 or 12 months of age between placebo, 1 mg of zinc and 5 mg of zinc supplement (12 months MDI: 1 mg zinc 107, SD 11; 5 mg zinc 107, SD 12; placebo 109, SD 12; p = 0.6) [28].

Iron supplementation has been investigated in a small trial of LBW infants born weighing <2,500 g. Fifty-eight infants were randomized to receive a high-iron-containing formula (21 mg/l) compared with formula containing 13.4 mg/l [30]. The infants’ neurodevelopment was assessed using the Griffiths Developmental Assessment at 3, 6, 9 and 12 months of age, with no significant difference found at any time point (12 months DQ higher iron 118, SD 11 vs. control 118, SD 10, n = 42).

**Long-Chain Polyunsaturated Fatty Acids**

Supplementation of infant formula with LC-PUFA for preterm infants has been the focus of two recent systematic reviews [31, 32]. Both reviews found that supplemented formula had no significant effect on DQ compared with no supplementation. At 12 months’ corrected age in a meta-analysis of 4 trials including 364 preterm infants, the WMD in BSID MDI was 0.96 (95% CI: −1.42 to 3.34) [31]. At 18 months’ corrected age, a 2.4-point improvement in DQ was found, but again this was not significant (95% CI: −0.33 to 5.12) [31].

Different versions of the BSID were used in the included trials, and because of this, Smithers et al. [32] conducted a subgroup analysis according to BSID version. The second version of the BSID included more language and problem solving items for 12- to 18-month-old children. This, along with differences in scoring and administration, may have introduced systematic differences in assessing neurodevelopment [32]. Accordingly, when trials using the same version of the BSID were considered as a separate subgroup, the cognitive DQ of LC-PUFA-supplemented infants assessed using version II of the Bayley Scales was significantly higher than control [32]. The meta-analysis included 5 trials of 879 infants and demonstrated a mean difference in MDI of 3.4 points (95% CI: 0.56–6.31).

Beyond 18 months, only one study has followed children into early childhood to determine cognitive effects of LC-PUFA supplementation in infancy [33]. This
trial of 238 infants randomized to formula supplemented with 0.5% DHA as total fatty acids versus unsupplemented, given from enrolment to 9 months of age assessed children when 10 years of age. They found no difference in IQ but did find suggestions of sex-specific and diet-specific effects, i.e. girls who received supplemented formula performed significantly better at single word reading accuracy and spelling than girls who received unsupplemented formula. In infants who did not receive any breast milk, those who were fed supplemented formula performed significantly better on a number of cognitive outcomes including IQ than infants who received unsupplemented formula [33]. However, given the very large losses to follow-up (55%), interpretation and generalization is difficult.

Most preterm formula has been supplemented with LC-PUFA since early 2000. Of more current clinical relevance are two recent trials in which DHA doses reflective of the estimated in utero accretion rate were used [34, 35]. These trials also included infants fed human milk. Both trials reported improvements in neurodevelopment. Henriksen et al. [34] studied 141 very LBW infants (<1,500 g) and demonstrated an improvement in problem solving at 6 months’ corrected age (intervention 53.4, SD 7.0 vs. control 49.5, SD 9.5; p = 0.02; n = 105). In a further follow-up at 20 months of age, they showed no difference in MDI (intervention 103, SD 10 vs. control 101, SD 13, p = 0.4; n = 92) but reported a significant improvement in sustained attention in free play activities [36]. The small sample size and large losses to follow-up make interpretation difficult.

The best evidence comes from the largest trial [35]. Although there were no significant differences in overall cognitive DQ at 18 months’ corrected age (MD 1.9; 95% CI: –1.0 to 4.7), girls had a significant 4.5-point (≈0.3 SD) improvement in cognitive DQ (95% CI: 0.5–8.5) [35]. In post hoc analyses, significant mental delay (MDI <70) was reduced from 10.5% in the control group to 5% in the higher DHA group (RR 0.50; 95% CI: 0.26–0.93). These children are currently being followed at 7 years’ corrected age to determine the effect of early LC-PUFA supplementation on cognitive outcome in early childhood. While suggestion of benefit is evident for LC-PUFA supplementation at 18 months of age, the long-term benefits of LC-PUFA supplementation in preterm children remain unclear.

**Conclusion**

LBW infants have well-documented cognitive deficits compared with their term, normal-birthweight counterparts. While it makes logical sense that at least part of these cognitive deficits may be explained by nutritional deprivation and that nutritional enrichment may improve the longer term neurodevelopmental outcomes of LBW children, few studies have been able to support this hypothesis. However,
the lack of support for the hypothesis linking nutritional supplementation and neurodevelopmental outcome is largely because the available studies were too small or had methodological shortcomings, limiting their ability to draw robust conclusions. Further large-scale rigorously designed intervention trials, with long-term neurodevelopment follow-up, are required to determine the optimal nutritional supplements and the timing of their administration to LBW infants.

Disclosure Statement

Maria Makrides serves on advisory boards for the Nestlé Nutrition Institute, Fonterra and Danone, and associated honoraria are paid to her institution to support the continuing education of early and mid-career researchers. Robert Gibson serves on advisory boards for Fonterra, and associated honoraria are paid to his institution to support the continuing education of early and mid-career researchers. For Carmel Collins and Amanda Anderson, there are no financial or other conflicts to report.

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