Evaluation of the Growth of Preterm or Low Birth Weight Infants Fed New Infant Formulas

A White Paper

Prepared for the Food Advisory Committee on Infant Formula
Food and Drug Administration

by

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November 18, 2002

This discussion will address two questions: What evaluation of growth should be required for a new formula developed for infants who are preterm (<38 weeks gestation) or low birth weight (LBW;<2500 g)? What other assessments, if any, are needed to adequately understand the effects of the growth rate sustained by this formula? For the purposes of this discussion, a new formula is one that is considered to differ in any important way from formulas that are conventionally fed to preterm infants.

Important relevant issues are discussed below in an order intended to promote a practical, rational, and to the extent possible, evidence-based approach to addressing the above questions:

1. Can the growth of infants fed this formula be adequately assessed by comparison to published growth "norms" for preterm or LBW infants?

Many studies of the growth rate of preterm infants have been published.[1,2,3,4,5,6] The growth curves published by the NICHD Neonatal Research Network[7] were based on serial measurements performed by research nurses in assessing a large sample (n=1660) of infants of very low birth weight infants (VLBW; ≤1500 g). Separate curves are provided for weight, length, head circumference, and midarm circumference with the average values plotted against postnatal age for infants in 100 g birth weight (BW) increments (starting at 501 g). Curves indicating the expected growth for individual infants can be generated at the Network website (http://neonatal.rti.org) by simply entering the infant's values at birth. The Network curves do not apply to infants greater than 1500 g BW or to infants after discharge home. Data for growth to 3 years has been published for a large cohort of preterm LBW infants who were enrolled in the Infant Health and Development Program (n = 985 infants).[8,9,10,11] While these data appear to be the best available, the findings are somewhat dated (the infants having been enrolled in 1985), and only a modest number of infants less than 1000 g were studied.

Despite such limitations, growth curves from these or other observational studies are useful to experienced clinicians in gauging the growth of individual infants. However, it should not be assumed that data from observational studies are suitable for assessing the growth supported by a new formula for preterm infants. For the latter purpose, one needs to precisely compare the growth sustained by this new formula to that sustained by conventional formulas for preterm infants. Many factors can compromise the validity and generalizability of observational studies for assessing infants subsequently fed a new formula. These factors include:

- measurement error (particularly for length and head circumference of sick infants) if the growth "norms" are based on clinical records,
- effects of parenteral as well as enteral nutrition on growth rates,
- temporal changes in care and outcome since the observational studies were conducted
- intercenter differences in population, including differences due to selection biases that affect the referral of high-risk mothers and infants,
- inter- and intracenter differences in obstetric practice, particularly those that might affect later growth (e.g. variation in using antenatal steroids and in managing the growth restricted fetus),
- inter- and intracenter differences in aggressiveness of care for extremely small or premature infants,
- inter- and intracenter differences in the routine feeding and care of preterm infants (e.g., differences in age at initiating and increasing feedings, administration of parenteral nutrition, regulation of thermal environment, use of postnatal steroids, etc.),

- intercenter differences in disorders affecting growth (e.g., necrotizing enterocolitis, chronic lung disease, intracranial hemorrhage, hydrocephalus, cortical atrophy, or cystic white matter disease). Differences in central nervous system complications may affect feeding and nutrient intake and certainly cause difficulty in interpreting "growth" in head circumference as a measure of the effect of nutrient intake, and
- intercenter differences in care after nursery discharge

For these reasons, the use of growth "norms" for preterm infants is clearly not a satisfactory basis to assess the growth of preterm infants fed a new formula.

2. Should carefully designed randomized trials be required?

Even in prospective studies, many of the above factors might bias the findings. When the investigators and/or the sponsors have a financial interest, it is particularly important to avoid the opportunity for bias the results. To minimize bias and random error and to increase the "signal to noise" ratio, stringent methodological features are needed. These include randomized assignment to the new formula or conventional preterm formula, blinded caregivers and evaluators, well standardized assessments, effective procedures to avoid patient loss, predefined stopping rules, and an adequate sample size and statistical power[12,13] (see below).

The feasibility of such trials has been enhanced by the establishment of a variety of neonatal research networks in the U.S., Canada, and other countries. The feasibility of these trials is also increased by the recognition that a relatively simple study protocol—that of a management trial--is appropriate for addressing questions like the effect of infant formula on growth, development, or health. Management trials (also known as effectiveness trials) are performed to evaluate the effect of an intervention under usual ("real world") clinical conditions. In such trials, it is not usually appropriate to control (or attempt to control) for other variables, (e.g., parenteral nutrient intake, total caloric intake, total fluid intake, thermal environment, ventilator management, etc. in a trial to assess the effects of a formula as it is used clinically). Partly for this reason, the cost/patient in management trials is usually substantially lower than in traditional explanatory trials (efficacy trials), trials designed to assess an intervention under ideal or restricted circumstances or to define the mechanism of its effects.[14,15] (In developing and evaluating a new formula or other intervention, a number of small explanatory trials may be needed before determining whether a large management trial is justified and how it should be designed.)

Partly for this reason, a proper trial to assess the effect of a new preterm formula on growth to discharge would be both highly desirable and reasonably feasible. Whether it is necessary and feasible to include a group feed their mother's milk or to assess later growth and development is addressed below (items 4, 5, and 7).

3. What infants should be enrolled? Who should be excluded?

The population studied should be that for whom the formula was prepared or at the highest risk infants of this population. While it would be appropriate to exclude the small subgroup of infants with major congenital anomalies, it would be inappropriate to exclude SGA infants, twins, or infants with major illnesses or complications. Such infants make up a large proportion of small survivors, and the benefits or hazards of new formula may be particularly important for them.

4. Should infants who are fed their mother's milk be included?

Many small preterm infants who receive formula also receive mother's milk for at least a short time. For this reason it is desirable to include such infants in separate strata and randomize them to feedings of new or conventional formula when an adequate supply of the mother's milk is not available. Some infants receive all or virtually all of their feedings from mother's milk although these infants can not identified at enrollment. Their inclusion affords an opportunity to compare the effects of formula and human milk feedings for preterm infants. (To the extent possible, such a comparison requires adjustment for potential confounders.)

5. What assessments should be performed?

Depending on the composition of new formula, its differences from conventional formulas, and the anticipated benefits and potential hazards, an assessment of body composition or biochemical, physiologic, or functional variables might be needed for all or a sample of infants in the management trial. Alternatively, these variables might have been adequately assessed in previous explanatory studies.

Possible adverse effects on health, e.g., an increased risk of necrotizing enterocolitis, should be assessed. If new formulas intended to augment growth are fed to infants with chronic lung disease, it would be particularly important to address potential adverse effects when there is marginal pulmonary sufficiency.

Assessments of the change in weight, length, and head circumference are obviously needed in evaluating growth. Skin fold thickness and mid-arm circumference[7] may also be considered.

There would also be strong justification for follow-up assessments of developmental, neurologic status, and health. The emphasis on assuring adequate growth rates in preterm infants is based in large part on long standing concerns about the effect of early nutrition and growth on the developing brain.[16,17] While "good" growth rates have generally been associated with favorable development, specific nutritional interventions, like other perinatal interventions, might differentially affect growth and development[18,19] or have unanticipated adverse effects on development or health. Such effects could conceivably occur through variety of direct or indirect mechanisms (e.g., amino acid imbalance, increased ammonia levels, acidosis, increased incidence of necrotizing enterocolitis, increased carbon dioxide production or marginal oxygenation in infants with pulmonary disease, or as yet undefined mechanisms of adversely affecting outcome). These effects would not be identified without careful follow-up evaluation.

Another reason to include follow-up assessments of health and development is to better define the optimal growth rate for preterm infants and the growth rate that preterm formulas should be designed to promote. This issue can not be resolved in observational studies which are unavoidably plagued by social and medical confounders. It can only be well addressed in experimental studies assessing neurodevelopmental and health of preterm infants randomly assigned to different nutritional regimens that result in different rates of growth.

6. What is the minimum period of assessment needed?

Because early growth may have long-term effects and because long-term growth deficits are common in preterm infants, it would be highly desirable to assess growth to no less than 18 to 24 months adjusted age (past term). This is an age when major developmental or neurological deficits may first be reliably identified.[20] Very long-term follow-up would not be justified for the routine evaluation of new or modified formulas. However, funding for long-term follow-up would

be highly desirable for research purposes, in part because of the ongoing controversy about whether low rates of growth in early life contribute to adult diseases.[21,22,23]

7. Based on what is currently known, what standard(s) should be used in judging whether the growth of preterm infants fed a new formula is more desirable, less desirable, or equally desirable as that of similar infants fed a conventional preterm formula?

The American Academy of Pediatrics has suggested that the goal of feeding preterm infants is to achieve postnatal growth approximating that of a normal fetus of the same postconceptional age.[24,25] However, this approach involves a number of problems:

A. Some uncertainty about intrauterine growth rates. These rates have been inferred from cross sectional studies relating BW to gestational age at delivery. Yet, different studies differ in the median and mean BW at each week of gestation and in the extreme values (e.g., the 10th and 90th percentiles) used to define small or large for gestational age infants at that week. These studies also differ in the slope of the regression line relating mean or median BW to gestational age and used to estimate fetal growth rates. These differences are due in part to problems in assessing gestational age by either pediatric or obstetric methods.[26] Errors in estimating gestational age from menstrual history are common and tend to result in underestimates of the true gestational age of preterm infants.[27,28,29] This problem artifactually increases the mean value and particularly the highest values ($\geq$90th percentile) for BW at the assigned gestational age among preterm infants. It also flattens the curve relating mean BW to gestational age prior to term and thus somewhat reduces estimated rates of intrauterine growth.

Some studies have addressed this problem by sophisticated statistical adjustments,[30,31] most notably in the recent population based Canadian study published by Kramer and colleagues.[32] The findings of these studies are more plausible for biological as well as statistical reasons than are the findings for studies that do not include such adjustments.

In principle, intrauterine growth would be better assessed from longitudinal assessments of fetal weight estimated sonographically in an unselected population than from cross sectional evaluations of BW among the subgroup of infants who deliver prematurely. In practice, however, sonographic assessments have had limited validity and reliability.[33,34] Until this problem is solved, intrauterine rates of weight gain will continue to be estimated from grids relating BW to gestational age. Because of the problems associated with preterm delivery, the mean or median weight at birth among preterm infants is likely to be somewhat lower than the weight for fetuses at the same postconceptional age.[35] If so, intrauterine growth rates estimated from the difference between mean or median BW prior to term and at term would be somewhat inflated.

B. Incomplete catch-up growth. Once preterm infants reach full feedings, current formulas for preterm infants do sustain postnatal growth rates that are comparable to estimated intrauterine growth rates at the same postconceptional age.[7,36] Nevertheless, with the initial weight loss prolonged period of illness and limited parenteral or enteral intake, infants less than 1500 g BW, particularly those less than 1000 g BW, often do not "catch up." As a group, they tend to remain permanently lighter and shorter than are infants who were born at term.[37,38,39,40] A slow rate of growth in the neonatal period may predispose to the development of sepsis or other neonatal complications and may have lasting unfavorable complications in later life.[32,41]

For these reasons, the goal for feeding preterm infants formulas might be modified to achieve complete or near complete catch-up growth. At least for the period between nursery discharge and one year, this goal is in accordance with those noted by Nutrition Committee of the Canadian Pediatric Society.[42] However, it is important to show that nutritional interventions

that sustain these growth rates do not impose undue risks or hazards, particularly when they are fed during periods of ongoing illness.

C. Potential adverse effects of feeding high-risk infants formulas that are intended to promote rapid growth. The relationship of nutrient intake to the occurrence of necrotizing enterocolitis remains to be resolved.[43] However, use of formulas intended to promote faster growth could increase the incidence of this serious disorder in high risk infants.[44] Another disorder of special concern is chronic lung disease, a common problem in small infants. In the Neonatal Network, 23% of VLBW infants have developed chronic lung disease. As BW decreases this percentage increases up to 62% among survivors 501-600 g BW.[45] Among infants with severe chronic lung disease, relatively slow rates of growth might be adaptive, and rapid rates of growth might not be achievable or desirable. Moreover, the appropriate nutrient mix at a specific caloric intake and the potential hazards of new formulas may well be somewhat different for these infants than for infants without chronic lung disease.[46,47]

8. How many infants require study to adequately assess a new preterm formula?

The answer to this difficult question will have a major effect on the time, cost, and effort required to assess a new formula, particularly if follow-up assessments are required as recommended above. This question will be addressed at length, in part because new approaches to the calculation of sample size or to the statistical evaluation of benefits and risks may be needed to test a new preterm formula (or other interventions) in a manner that is both feasible and valid.

When a new formula is considered sufficiently promising to justify a management trial, there may be strong *a priori* reasons to believe it would preferable to a conventional formula. For example, a new formula may contain a component that has not been available in conventional formulas but is a nutrient that is normally received from the mother before birth and in human milk after birth and that may well promote optimal growth, health, or development. However, even when there seem to be compelling rationale for a new formula, it would be important to exclude the possibility of important unexpected adverse effects.

Major adverse effects to "rule out." At the current time, the following can be considered to be important adverse effects:

A. An absolute increase in necrotizing enterocolitis (NEC) (or perhaps other major adverse clinical outcomes) of 3-7% or greater.

NEC is a serious, often life-threatening neonatal illness, particularly in small preterm infants. A 3% increase would correspond to a "number needed to harm" of 33 infants (that is, feeding the formula would cause one infant to develop NEC for every 33 infants fed the formula).[48] Although it is difficult to determine the level of treatment hazards that are considered acceptable, this might be considered unacceptable by clinicians (if not parents) even if all infants who did not develop NEC had more rapid growth or even improved development. A 5% increase, corresponding to a number needed to harm of 20, would undoubtedly be considered unacceptable by clinicians. A 7% increase (corresponding to a number needed to harm of 14) would be particularly unacceptable to clinicians. (A similar magnitude of increase prompted early termination of a trial assessing an intervention likely to reduce chronic lung disease in small preterm infants. [49]) A 7% increase would result in a doubling of the incidence of NEC in VLBW infants in the Neonatal Network. [50]

B. A reduction in mean growth to nursery discharge or at follow-up of 0.25 SD or greater among VLBW or ELBW infants.

At least after recovery from serious illness, there would seem to be no reason to consider slow growth to be desirable. Because of the persisting growth deficits of small infants and the association of impaired growth with other adverse outcomes among these infants, even a modest reduction in growth among infants fed a new formula (relative to that of randomized controls fed a conventional preterm formula) can be considered presumptive evidence of harm. A reduction in growth of either head circumference or length would be of particular concern.

C. A reduction in mean developmental quotient at 18 months or later (or in intelligence quotient at 3 years or later) of 0.25 SD or greater.

A difference of this magnitude in cognitive development would have substantial and important effects on the proportion of children born prematurely who would be classified as intellectually deficient or of borderline intelligence.[51] One might argue to use a larger deficit in order to reduce the sample size required for testing a new formula. However, nutritional effects resulting from different formulas are unlikely to be any larger. The difference between preterm infants and term infants due to all causes (including hypoxic episodes, intracranial hemorrhage, etc.) is approximately 0.67 SD.[52] The largest nutritional effects on development of preterm infants reported in recent, well conducted studies have been approximately 0.25 SD.[16-18] In one study, children who were preterm and fed maternal milk had an intelligence quotient that was 0.5 SD higher than among preterm infants fed formula, after the difference was adjusted for known potential confounders.[17] However, because it is impossible to accurately measure and adjust for all potential confounders, this is likely to be an overestimate of the true effect. Among unselected populations generally born at term, breast feeding has been associated with an advantage of 0.33-0.5 SD difference in intelligence quotient after adjusting for measured potential confounders.[53,54]

Number of patients needing study in randomized trial(s). If the same infant formula is studied in multiple small trials with a similar design, meta-analysis may be used where appropriate to aggregate the results in a state-of-the-art fashion. However, performing a single large trial is preferable to multiple small trials, in part because it avoids the problem of publication bias and generally reduces concerns about trial design, oversight, and analysis. Conventional and innovative approaches to determining the sample size for such a trial are noted below.

A. Calculate sample size using the conventional approach.

In a trial designed that assess infants only to nursery discharge, an enrollment of 252 patients per group would be required to identify a difference between two formula groups of 0.25 SD in mean weight gain (or gain in length), as analyzed using a 2-tailed test with an alpha error of 0.05 and a power of 0.80. (This sample size was calculated using NCSS software assuming the data compatible with the assumptions of the t test). For reasons noted above, a trial that extends to age 18 months or older would be preferable. Allowing for as much as a 20% loss to follow-up, enrollment of 315 infants per group would be needed to identify a difference of 0.25 SD between groups in mean growth or in developmental quotient at that age. This sample size would also allow a reasonable chance of identifying an important adverse effect on NEC. At a 7% baseline incidence of NEC, assessment of 315 infants in the neonatal period would allow 78% power to identify an absolute increase of 7% and 52% power to identify a 5% increase. There would clearly be inadequate power (22%) to identify a 3% increase (two tailed test).

To achieve 90% power to identify a 0.25 SD difference in developmental quotient (or growth) at 18 months would require 421 infants in each group provided no more than 20% of infants were lost to follow-up. This sample size would afford excellent power (89%) to identify a 7% increase in NEC, and reasonable power (65%) to identify a 5% increase. It would allow only 30% power to identify a 3% increase. Nevertheless, given the expense of follow-up to 18 months (roughly $1000-2000 per patient), formula manufacturers may be unwilling to undertake a randomized trial that would involve 421 infants per group.

In considering this and the trial design below, it should be noted that sequential analyses can be performed to allow early termination of the study if there is convincing evidence of benefit (or harm) is obtained. Of course, the appropriate statistical adjustment is needed for repeated "peeks" at the data.

B. Perform a noninferiority trial.

If there are strong *a priori* reasons (as noted above) to consider the new formula preferable to the old, the clinical trial might be designed as a noninferiority trial.[55,56] This approach could allow a somewhat smaller sample size and thus a less expensive study than with a conventional design.

The objective of such a noninferiority trial would be to show that at worst, the outcome with the new formula would be clinically acceptable, e.g. any reduction in developmental quotient would be less than 0.25 SD. Such a finding would almost certainly be accompanied by a higher mean developmental quotient among infants fed the new formula than among infants fed the conventional formula. In the noninferiority trial, the new formula could be recommended even if the increase in mean developmental quotient were not statistically significant as long as the lower limit of the 95% confidence interval was better than -0.25 SD. In a conventional trial, the new formula would be recommended only if the difference were statistically significant, that is if the lower boundary of the 95% confidence interval exceeded a value of zero.

Using this approach, the sample size (allowing for up to 20% loss to follow-up) would be 249 per group to achieve 80% power (66 per group fewer than with the conventional approach); 344 per group would be needed to achieve 90% power (77 per group fewer than with the conventional approach). Unfortunately, the reduction in sample size is not particularly large (less than 20%), and there would be limited power to identify a statistically significant increase in NEC at the p value (likelihood of an alpha error under the null hypothesis) that is ordinarily considered to be significant ($p<0.05$). However, the formula might still be recommended provided the direction of any difference between the groups favored the group fed the new formula. If not, the trial could not be considered adequately definitive.

C. Accept a higher alpha error for predefined treatment hazard(s) (irrespective of whether a conventional or noninferiority trial is performed).

By convention, a $p<0.05$ has been used to indicate statistical significance in the great majority of clinical studies. However, this practice is arbitrary and unreasonable. For a variety of reasons discussed elsewhere[15], clinical studies are likely to be biased in the direction of identifying benefit and of failing to identify harm. Partly for this reason, a $p<0.05$ is a reasonable requirement before investigators are allowed to proclaim benefit. However, it does not follow that treatment hazards should be considered to be excluded at a $p>0.05$. The p selected as indicating statistical significance should depend in part on the "cost" of being wrong. For a life-

threatening hazard like NEC, one might accept a high alpha error—perhaps a p value (defined prior to study) as high as 0.30 or even higher —to minimize the likelihood of recommending a formula that caused this problem. Willingness of the investigators to accept such a relatively high p value would decrease the sample size requirements to address both benefits and hazards.

D. More precisely define the acceptable ratio of patients harmed to patients benefited and compare this ratio to that observed in trial (and the 95% confidence limits).

This is a cutting edge issue in evaluating and interpreting the results of clinical research. Page limitations preclude discussion of this issue. However, see the work of Sinclair and colleagues[57] in deriving the threshold number needed to treat, a measure that combines treatment benefits and hazards and the baseline prevalence of adverse outcomes for use in determining when the best evidence indicates that an intervention--such as a new preterm formula--should be used.

The above considerations indicate the possible problems in evaluating a new preterm formula. Nevertheless, these difficulties can be considered well worth addressing in order to better promote the long-term growth, development, and health of small preterm infants. Although well designed management trials do not always provide definitive results, they afford the best opportunity for a precise and unbiased assessment of new preterm formulas and in assuring that their benefits outweigh their hazards.

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