Evaluation of Growth and Early Infant Feeding: A Challenge for Scientists, Industry and Regulatory Bodies

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Abstract

Growth studies are necessary to prove safety and efficacy of new or renovated infant formulas. Healthy infants need to be followed in randomized clinical trials until 4–6 months of age. Breastfed reference groups should be included in such studies, because growth of formula-fed infants may deviate from breastfed infants. The WHO growth standard describes growth of exclusively or predominantly breastfed infants and is frequently used as reference. However, the limitations of the standard must be known because weight-for-age until 6 months is higher than in all international growth references. Meta-analyses indicate that both weight and BMI of breastfed reference groups in clinical trials and of infants fed a low protein formula are somehow lower than the WHO standard. Infants of overweight and obese mothers or at risk for malnutrition are considered as at-risk populations. Any infant formula trial in those populations should use the WHO standard to document safety.

To prove the safety and efficacy of infant formulas fed to healthy and at-risk infant populations, scientists are conducting randomized clinical trials which are sponsored by manufacturers. Trials have to be registered and dossiers have to be reviewed and approved by regulatory agencies (e.g. FDA, EFSA) before a new product can be introduced. Growth studies should include the period of exclusive feeding of a new or renovated infant formula (i.e. until 4–6 months of age). A long-term follow-up is under debate. Until 2006, when the WHO growth standards (1, www.who.int/childgrowth/en/) were published, growth (weight, length, head circumference, BMI) was compared of infants who were fed the new/renovated formula, a standard
product on the market, and a breastfed reference group. The WHO growth standard, which describes growth of exclusively or predominantly breastfed infants from different countries living in a favorable environment [1] indicate that growth of breastfed infants differs from international growth references [2–4]. Those references are based both on breastfed and formula-fed infants. In particular, weight of the infants from the WHO standards is higher until 6 months of age. During the second half of the first year and the second year, the weight of the WHO standards is lower. If new formulas are tested it is therefore important to select the ‘right reference’ for comparison. In infant populations with high risk of obesity or malnutrition, the question related to the ‘right reference’ is even more difficult to answer. It is not clear if growth data of exclusively breastfed infants from those at-risk groups provide adequate references.

**Breast-Fed Reference Groups (Clinical Trials) versus WHO Standards**

The WHO growth standards [1] which were created with the best intentions are the only globally representative standards, even when Asian infants are missing with the exception of an Indian cohort (probably partially Caucasian infants). The majority of newborn infants worldwide come from Asia. The WHO weight-for-age curves for the first 4–6 months are higher than the corresponding curves of international growth references [3, 4]. This is surprising because breastfed infants tend to grow slower than formula-fed infants [2]. However, only 50% of the infants enrolled at birth into the WHO growth study completed the study as planned. It can be speculated that many infants had to leave the study because the mothers wished to provide complementary feedings or quit breastfeeding [2]. It is well documented that mothers are more likely to introduce complementary foods earlier if weight gain of the infant is low [4, 5]. Selective dropout is the probable reason why the infants who remained in the WHO study are relatively large [2, 6]. The weight-for-age WHO standard until 6 months seems too high and perhaps unattainable for many healthy breastfed infants. This can create problems if growth studies with infant formulas are using the WHO standards for comparison. It would be helpful if WHO would provide an ITT analysis (data from all infants who were enrolled in the study) or show how those infants are growing who are at least exclusively or predominantly breastfed until 6 months of age.

We compared weight at 4 months of age of breastfed reference groups (randomized clinical trials) with the WHO standards. In a meta-analysis, we identified 4 recent trials with complete data sets on weight and BMI. The age of 4 months was selected for comparison with the WHO standard because many infants on the trials received complementary foods after 4 months of age. Indeed, both weight (fig. 1) and BMI (–0.28; CI –0.42, –0.14) z-scores of the infants in the 4 trials were lower, in particular in Europe.
Formula-Fed Infants in Clinical Trials versus WHO Standards

It has been shown that feeding high protein formulas results in higher weight during infancy and beyond [7]. Higher weight gain during infancy is associated with overweight during childhood and adolescence, which is a predictor of adult obesity [8]. A modern whey-based formula with a lower protein concentration of 1.8 g/100 kcal (NAN) has received regulatory approval and is on the market in the EU and many other countries [9, 10]. It was therefore of interest to compare weight and BMI of infants fed those low protein formulas with breastfed reference groups, an international growth reference for breastfed infants [5] and the WHO standard [1]. Weight and BMI at 4 months, when exclusive formula feeding ended, were similar in infants receiving the low-protein formula, the breastfed reference groups and the Euro-Growth references for breastfed infants [5]. When compared by meta-analysis (5 RCTs) with the WHO standards [1], infants fed the low protein formula at 4 months of age tended to have lower weight (fig. 2) and had significantly lower BMI (z-scores −0.32; CI −0.57, −0.06).

Should we therefore use the WHO growth standards to evaluate growth of healthy formula-fed infants living in a favorable environment? The advantage of the WHO growth standard is that it is global and recognized by regulatory agencies in most countries of the world. As long as the researcher and the regulatory agency is informed that the WHO weight for age standard until 6 months is higher than international references, there should be no problem. It should also be mentioned that growth of breastfed reference groups which are followed in a clinical trial might be influenced by earlier introduction of complementary foods than planned and/or introduction of formula feeding.
Breastfed Reference Groups in Study Populations at Risk for Malnutrition (Obesity, Undernutrition)

Testing safety and efficacy of infant formulas in at risk groups also requires comparison with breastfed infants. According to the ‘metabolic programming’ hypothesis, infants from obese mothers might be at risk to have a higher birth weight and high weight gain during infancy [8]. According to the hypothesis, intrauterine exposure to an excess of fuels (e.g. glucose) causes permanent changes of the fetus that might result in obesity later in life. The accelerated postnatal weight gain hypothesis assumes an association between rapid weight gain in infancy and an increased risk of later obesity and adverse outcomes. When clinical trials are designed to test formulas in infants of overweight or obese mothers it has to be decided to include either a breastfed reference group from respective mothers or to use the WHO references. In an ongoing infant formula clinical trial, we followed a breastfed reference group of overweight and obese mothers. Weight and BMI at birth, 3 and 6 months of age (z-scores; table 1) were significantly higher than the corresponding WHO standards. No prospective studies with long-term outcome are in the literature and the reasons for higher intrauterine and postnatal weight of breastfed infant cohorts of overweight/obese mothers still needs to be studied. Our findings are in accordance with the ‘metabolic programming’ hypothesis, which proposes that epigenetic modifications in infants from obese mothers could be responsible for the higher pre- and postnatal weight [8]. In any case, studies in infants of obese mothers should use the WHO growth references for comparison.

In developing countries, in particular in those with a high burden of maternal HIV disease, testing safety of any formula in the target population is a must. In South Africa, randomized clinical trials [11, 12] were done to test the safety of a new...
acidified formula in infants of HIV-positive mothers who could not breastfeed. Those infants are high at risk to become malnourished. It was impossible to enroll a breastfed control group. Therefore, only formula-fed groups were compared in that trial. Comparison of weight, length, and BMI with the WHO standards now shows that the cohort of formula fed infants was growing parallel to a percentile channel, which is a good safety indicator. However, it should be mentioned that the cutoff values (e.g. 3rd percentile for weight for age) of the WHO standards are different from international growth references [13]. It is therefore difficult to compare the percentage of malnourished infants in growth studies, if different international standards/references are used.

Conclusions

Randomized clinical trials to study safety and efficacy of infant formulas in healthy infants should include a breastfed reference group. Infant formula studies in at-risk infant populations should use the global WHO growth standard for comparison, but the researchers must be familiar with its limitations.

References


Table 1. Weight and BMI (z-scores) of breastfed infants of mothers who are overweight or obese versus WHO standard

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth (n = 76)</td>
<td>+0.55</td>
<td>+0.48</td>
</tr>
<tr>
<td>3 months (n = 76)</td>
<td>+0.67</td>
<td>+0.76</td>
</tr>
<tr>
<td>6 months (n = 65)</td>
<td>+0.89</td>
<td>+1.04</td>
</tr>
</tbody>
</table>

All values are significantly higher than the WHO standard.


