# Retrospective Cohort Study of a New Infant Formula during the First 6 Months of Life: Reflections on Growth Curves, Human Milk and Formula Feeding

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**ABSTRACT:** **Background:** Optimil® is an infant formula, manufactured in Israel and introduced to the market in May 2008.

**Objectives:** To assess the effect of this formula on infant growth.

**Method:** The study group comprised 52 infants who for the first 6 months of life consumed Optimil, which constituted at least 25% of their total daily intake. Anthropometric data were collected from the records of the well-baby clinics. Weight, length and head circumference at baseline and 3 months thereafter were converted to gender and age-matched standard deviation *Z*-scores. As an exploratory uncontrolled analysis, questionnaires were sent to the caregivers to assess satisfaction with the formula and to note the rate of constipation, irritability and vomiting as well as apparent palatability.

**Results:** The baseline *Z*-scores of all three parameters were below zero but increased significantly after 3 months (-0.2 ± 0.88 to 0.12 ± 0.88, $P = 0.013$ for weight; -0.44 ± 0.87 to 0.10 ± 0.72, $P < 0.001$ for length; and -0.58 ± 0.78 to -0.1 ± 0.76, $P < 0.001$ for head circumference). There was a significant dose-response effect of the formula with weight gain. The formula was generally well accepted, with 8% constipation, 8% vomiting and 6% significant irritability.

**Conclusions:** This study provides the first evidence that infants consuming Optimil under age 6 months have adequate growth. Nonetheless, breastfeeding during this period should be preferred in almost all cases.

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**KEY WORDS:** growth, infant, Optimil®, formula, tolerability

Human milk is considered the preferred diet for almost all newborns. However, since breastfeeding is not always feasible or desired, formulas have been developed to mirror, as much as possible, human milk. Optimil® (Medici, Raanana, Israel) is a newly marketed infant formula in Israel. It was developed according to the specifications of both the international Codex Alimentarius (available at: http://www.codexalimentarius.net/web/more_info.jsp?id_sta=288) and the European Directive in December 2006 [1], and has been commercially available in Israel since May 2008. While the exact composition of the formulas varies, they are all under the strict supervision of the Ministry of Health and adhere, in general, to the criteria developed by the Codex Alimentarius. However, these international standards leave some room for modification and may affect outcomes. For instance, formulas containing fat in the form of palm oil may be associated with higher rates of fecal fat and calcium losses, possibly resulting in constipation and reduced bone mineralization [2,3]. There are differences in the content of several additives not included as mandatory ingredients by the Codex such as probiotics, nucleotides, long chain polyunsaturated fatty acids and carbohydrates. It is possible that the differences between formulas may contribute to differences in infants' growth. However, local and international regulations do not mandate assessing the effect of infant formulas on growth.

The aim of this investigator-initiated, industry-funded, retrospective cohort study, was to evaluate, for the first time, anthropometric characteristics of a group of infants who consumed Optimil during the first 6 months of life. As a secondary and exploratory aim, data concerning tolerability were also recorded.

## SUBJECTS AND METHODS

This was a retrospective longitudinal cohort study of infants who consumed Optimal during the first 6 months of life. The study was approved by the institutional ethics committee.

The cohort comprised infants of caregivers showing interest in Optimil via house clubs, employee acquaintances and those who encountered the product via the company website. At inception, participating caregivers (154 households in total) provided informed consent to be contacted on a periodic basis for data collection in return for discount vouchers. A raw and complete list of these families was provided by

Medici. The list included all caregivers who participated in the monitoring program for any duration of time, in order to minimize selection bias.

### ELIGIBILITY

Infants who began on Optimil formula during the first 6 months of life for any length of time, exclusively or combined with other feeding but more than 25% of total intake, were included. Only one infant per household (the oldest) was included to avoid bias of repeated measures. Infants with significant morbidities that may affect growth (such as congenital anomalies and metabolic disease) were excluded.

### STUDY PERIOD

The study period was defined as the 3 month period that began when Optimil constituted at least 25% of the infants' total daily intake (as estimated by the caregiver). Being a potential confounder, the amount of Optimil consumed during that period was included in the analysis below.

### DATA COLLECTION

We collected data on the following: basic demographics, comorbidities, explicit feeding pattern and type since birth, stool consistency (using the Bristol stool chart), straining during defecation, the need for anal stimulation, degree and duration of irritability, palatability (scored by a 5 point FACES scale), and presence of vomiting. A structured questionnaire to capture these data was developed following review of the literature. The final draft was pretested on several volunteer mothers unrelated to the present study who were probed for coherence and validity. A revised draft was retested on additional mothers until no further issues were identified. Response burden was evaluated by measuring the time to completion of each question. All anthropometric data were collected from the prospectively maintained records of the Israeli public health well-baby clinics (mother and child health clinics, known in Israel as *Tipat Halav*).

### OUTCOMES

*Primary (anthropometric data):* The primary outcome was growth (i.e., length and weight gain) from baseline (at the time of Optimil initiation) to the end of the 3 month period. All anthropometric measures were transformed to standard deviation scores (SDS or *Z*-scores). Length and weight were compared to the calendar age and gender-matched reference standards published by the Centers for Disease Control's National Center for Health Statistics in 2000, utilizing the LMS method described by Cole and Green [4].

- A $\Delta Z$-score (i.e., follow-up *Z*-score minus baseline *Z*-score) was calculated to identify cases crossing percentiles. A $\Delta Z$-score > 0 means catch-up growth and $\Delta Z$-score < 0 reflects failure to thrive (i.e., any deviation from 0 means crossing percentiles). One of the methodological challenges of this study was that in most cases Optimil was not administered exclusively. The addition of breast milk, other formula or solid foods may confound the results, particularly since feeding patterns typically change over time. Therefore, a summary variable was calculated for each infant to reflect the overall Optimil exposure over time. The mean Optimil intake out of the total daily intake was expressed as the weighted percent intake calculated during the study period and expressed as "Optimil factor" with a range of 0 to 1, where '0' signifies no Optimil at all throughout the 3 month period, and '1' indicates an exclusive Optimil diet. To assess the dose-response effect of Optimil exposure on growth, analyses were also stratified according to this "Optimil factor."
- *Secondary outcomes:* In view of the lack of a control group, possibility of recall bias, selection bias, and response bias of caregivers who received a discount on the formula, these outcomes should be considered as exploratory in nature and should not be used to elucidate any conclusions. The following secondary outcomes were assessed: the presence of constipation (i.e., stool consistency, straining during defecation and the need for anal stimulation), episodes of diarrhea or vomiting, irritability (reflecting overall health including the low likelihood for reflux esophagitis or infantile colic) and the palatability of the formula (scored on a 5 point Likert scale).

### STATISTICAL ANALYSIS

Data are expressed as proportions (with the corresponding 95% confidence intervals) means (± SD), or medians (interquartile range), as appropriate. For the primary analysis, the change in *Z*-score from baseline was tested by paired Student's *t*-test. Deviation of *Z*-scores from '0' was assessed using one-sample Student's *t*-test and correlations between growth and Optimil factor using Spearman's correlation coefficient. Non-parametric comparisons between more than two groups used the Kruskal-Wallis test. Chi-square or Fisher's exact tests were used to compare categorical variables. All comparisons were made using two-sided significance levels of $P < 0.05$. Statistical analyses were performed using SPSS for Windows V12.0.

## RESULTS

Of the 75 families approached 56 returned the questionnaires; and of these, 52 fulfilled the eligibility criteria and are included in the study (4 were excluded for the following reasons: 3 started Optimil after 6 months of age and 1 had concomitant significant illness) [Table 1]. Following the eligibility criteria, all infants started Optimal at an amount that was at least 25% of their intake before the age of 6 months (mean age 3 ± 1.8 months). Most (n=41, 79%) were on

another formula previous to Optimil for reasons shown in Table 1; the others were breast-fed.

In order to assess growth parameters during optimil intake, we transformed all anthropometric data to standard deviation scores (i.e., *Z*-scores). At the introduction of Optimil, the *Z*-scores were slightly below zero [Table 1], indicating that the median infants' weight and length were below the values as set by the CDC reference standards. This deviation from zero reached statistical significance for length (one-sample Student's *t*-test, $P = 0.003$) and circumference ($P < 0.001$) but not for weight ($P = 0.092$). The low baseline anthropometric values were independent of whether the infant was bottle or breast-fed ($P > 0.05$).

Three months after introducing Optimil, there was an increase in the *Z*-score values for weight (from -0.2 ± 0.88 to 0.12 ± 0.88, $P = 0.013$, paired Student's *t*-test); length (from -0.44 ± 0.87 to 0.10 ± 0.72, $P < 0.001$); and head circumference (from -0.58 ± 0.78 to -0.1 ± 0.76, $P < 0.001$) as compared with the baseline value [Figure 1]. When considering the *change* in *Z*-scores over this 3 month interval, all three parameters – weight, length and head circumference – increased significantly (one-sample Student's *t*-test, $P < 0.001$ for length and head circumference, $P = 0.013$ for weight). These figures mean that the included children showed catch-up growth, crossing growth percentiles upwards, while ingesting Optimil for 3 months. There was a clear dose-response relationship between the amount of consumed optimil and increased weight *Z*-scores [Figure 2].

The results of the satisfaction survey are shown in Table 2. The report of four caregivers (8%) was consistent with significant constipation (considering stool consistency, crying while defecating, and the need for rectal stimulation).

CDC = Centers for Disease Control

**Table 1.** Characteristics of children fed on Optimil before age 6 months

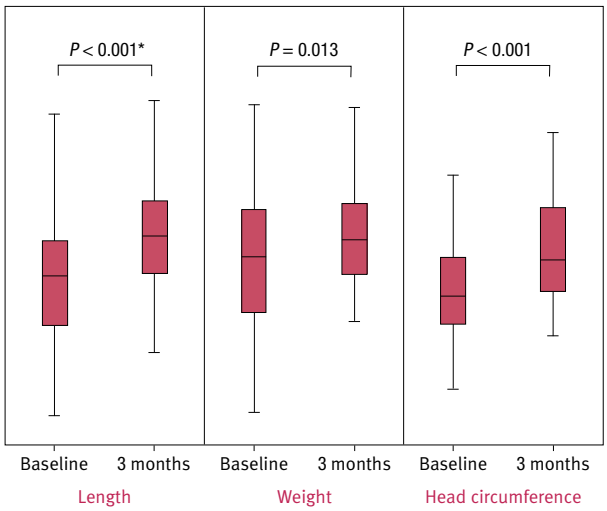
| | Total cohort (n=52) |
|---|---|
| Males | 24 (46%) |
| Age when starting Optimil (mos) | 3 ± 1.8 |
| **No. of bedrooms** | |
| 1–2 | 30 (58%) |
| 3–4 | 22 (42%) |
| **No. of residents in the house** | |
| 2–4 | 29 (56%) |
| 5–7 | 21 (40%) |
| ≥ 8 | 2 (4%) |
| Fed with other formulas previous to Optimil | 41 (79%) |
| **Reason of changing formula (n=39)** | |
| Dissatisfaction from previous formula | 8 (21%) |
| Marketing | 21 (54%) |
| Recommended by others | 5 (13%) |
| Appealing formula composition | 5 (13%) |
| Length *Z*-score (SDS) | -0.4 ± 0.9 |
| Weight *Z*-score (SDS) | -0.2 ± 0.95 |
| Head circumference (SDS) | -0.6 ± 0.78 |

Counts (%) or means ± SD are presented as appropriate for the data distribution.

## DISCUSSION

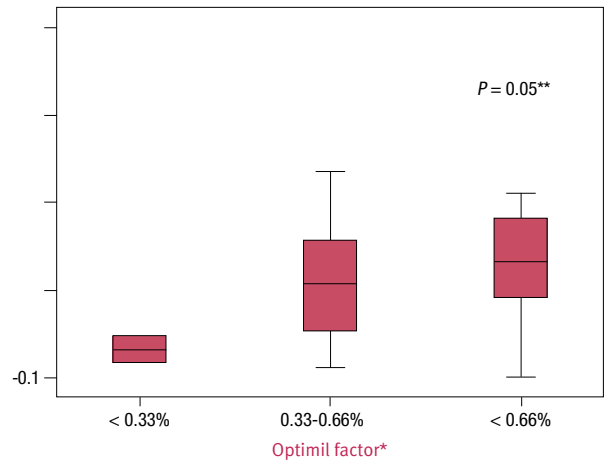
In this cohort study we found that infants who consumed Optimil during the first 6 months of life increased their median *Z*-scores for weight and length from below to above zero.

**Figure 1.** Anthropometric data at introduction of Optimil (baseline) and 3 months thereafter




*Paired Student's *t*-test

**Figure 2.** Change in weight *Z*-scores over 3 months, stratified by the amount of Optimil consumed




*"Optimil factor" reflects the average percentage of consumed Optimil from the total daily calories over the 3 month period.

**Kruskal-Wallis test (Spearman's correlation between Optimil factor and weight *Z*-score $r = 0.42$, $P = 0.003$)

**Table 2.** Results of the parents' questionnaire

| | Total cohort (n=52) |
|---|---|
| **Stool consistency** | |
| Diarrhea | 0 (0%) |
| Soft | 36 (69%) |
| Hard | 14 (27%) |
| Did not answer | 2 (4%) |
| **Straining during defecation** | |
| No | 28 (54%) |
| Yes | 24(46%) |
| **Need for anal stimulation for defecation** | |
| No | 41 (79%) |
| Rarely | 10 (19%) |
| Often | 1 (2%) |
| **Irritability** | |
| No significant irritability | 50 (96%) |
| Significant irritability (severe crying or moderate crying › 4 hours/day) | 2 (4%) |
| **Optimil palatability** | |
| Infant likes the taste | 49 (94%) |
| Neutral about the taste | 2 (4%) |
| Infant does not like the taste | 1 (2%) |
| **Vomiting** | |
| Never or insignificant | 40 (77%) |
| Rarely | 10 (19%) |
| Once a week | 2 (4%) |
| More than once a week | 0 (0%) |

In Israel, human milk substitutes are under strict regulation to conform to the International Codex and are under quality control. Since the Codex regulations leave some room for modification, infant formulas are not identical. For instance, the amino acid composition of bovine whey and casein varies significantly from that of humans, and in order to enable adequate supply of all amino acids, manufacturers have increased the protein concentration of the infant formula. This increase is associated with an enhanced growth pattern during the first 2 years of life as compared to infants fed on human milk [5]. The formula used in this study is unique in that it is supplemented with selenium at a concentration recommended by the European Directive. Selenium is an essential trace element that plays a key role in antioxidant and immune function, redox regulation and thyroid function [6]. Formulas without supplementation have endogenous selenium concentrations 30–50% lower than those in human milk [7,8]. These variations and others are potentially important for short and long-term health promotion, but solid evidence to support the choice of ingredients is scarce. It is reassuring that growth is adequate in infants who consume the newly marked formula.

The fact that the infants who started the study had *Z*-scores below zero warrants clarification. Since measurements were prospectively obtained by unbiased individuals (i.e., nurses from the well-baby clinics, uninvolved in the study), we have no reason to believe that there was a measurement bias. Most infants included in the study switched to Optimil from a different formula [Table 1]. Infants are more likely to be switched to a different mode of feeding if they are not growing well. However, only 20% of the infants were switched to Optimil because of parental dissatisfaction with the previous formula, and the baseline *Z*-scores did not differ between breast-fed and formula-fed infants. This argues against selection bias. It is possible that the CDC curves used in this study were not representative of the population under study. The current 2000 CDC curves [9,10] are significantly improved compared with the former curves from 1977 [11]: the current one is composed of approximately one-third breast-fed infants while the previous version comprised almost exclusively formula-fed infants. In addition, they represent a population of more recently born children (1971–94 versus 1929–75). Nonetheless, Israeli infants are expectedly different from those used to compose the CDC curves, 14% of whom are African-American. In 2006, the World Health Organization published a set of curves [12] based on primary data collected through the WHO Multicenter Growth Reference Study conducted between 1997 and 2003. The population-based MGRS study was conducted on individuals who lived in socioeconomic conditions favorable for "normal" growth [13]. However, using these charts would not have solved the issues outlined above for the CDC curves: de Onis et al. [14] showed that 226 healthy infants had a different growth pattern from both the CDC and WHO curves. These infants had higher *Z*-scores for weight compared with the WHO curves during the first few months of life but slightly lower scores at 7 months. In comparison with the CDC curves, elevated *Z*-scores were noted during the first 2 months of life but were significantly reduced at 12 months of age. The validity of both curves was similarly questioned by Van Dijk and Innis [15] who demonstrated that the growth data of 73 Canadian infants were systematically different from the WHO and the CDC standards and that these deviations were related to gender and the feeding mode.

Unfortunately, Israeli reference standards for growth are not available. Although the negative baseline *Z*-scores in this study do not necessarily reflect failure to thrive, it can be used effectively as a reference to the follow-up scores in the same infant. We found that there was a significant increase in the *Z*-score values for all anthropometric data after introducing Optimil. It is reasonable to conclude that the infants' growth was at least adequate. The obvious "dose-response" effect strongly supports this conclusion.

The secondary outcomes are vulnerable to all biases inherent to a retrospective design, including selection bias, recall bias and heterogeneity in the cohort. In addition, there may be a response bias as the families bought the product at a discount. The prospectively collected anthropometric data, chosen as the primary outcome, are much less exposed to the mentioned biases. From the exploratory results of our

MGRS = Multicenter Growth Reference Study

secondary outcomes, it seems that the formula was generally well accepted and that most parents felt satisfied. Additional meaningful comments would require a control group.

Obtaining methodical data on infant formulas is of utmost importance to the community. The small differences between the existing formulas merit evaluating their effect on clinical outcomes. The present work should be considered as a pilot study to generate basic data on clinical outcomes related to Optimil, not studied until now. Bearing in mind the potential biases, it may be concluded that growth is satisfactory in infants who consumed Optimil during the first 6 months of life.

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