Effect of a Low-Allergen Maternal Diet on Colic Among Breastfed Infants: A Randomized, Controlled Trial

David J. Hill, FRACP*; Neil Roy, FRACP§; Ralf G. Heine, MD, FRACP*¶; Clifford S. Hosking, MD, FRACP*; Dorothy E. Francis, APD*; Jennifer Brown, RN*; Bernadette Speirs, RN§; Joel Sadowsky, FRACP§; and John B. Carlin, PhD*¶

ABSTRACT. Background. There is controversy regarding whether hypersensitivity to food proteins contributes to colic among breastfed infants.

Methods. A randomized, controlled trial of a low-allergen maternal diet was conducted among exclusively breastfed infants presenting with colic. In the active arm, mothers excluded cow’s milk, eggs, peanuts, tree nuts, wheat, soy, and fish from their diet; mothers in the control group continued to consume these foods. Outcomes were assessed after 7 days, as the change in cry/fuss duration over 48 hours, with validated charts. The primary end point was a reduction in cry/fuss duration of ≥25% from baseline. Mothers also assessed the responses to diet with categorical and visual analog scales.

Results. Of 107 infants, 90 completed the trial (mean age: 5.7 weeks; range: 2.9–8.6 weeks; 54 male infants). Infants in both groups presented with significant distress (geometric mean: low-allergen group: 690 minutes per 48 hours; control group: 631 minutes per 48 hours). In follow-up assessments on days 8 and 9, there were significantly more responders in the low-allergen group (74% vs 37%), ie, an absolute risk reduction of 37% (95% confidence interval: 18–56%). Cry/fuss duration per 48 hours; control group continued to consume these foods. Outcomes were assessed after 7 days, as the change in cry/fuss duration over 48 hours, with validated charts. The primary end point was a reduction in cry/fuss duration of ≥25% from baseline. Mothers also assessed the responses to diet with categorical and visual analog scales.


ABBREVIATION. VAS, visual analog scale.

Infantile colic affects up to 28% of infants in the first months of life.1,2 Colic symptoms usually peak at ~6 weeks of age and improve gradually over the following weeks.3 In a recent Canadian study, 6.4% of infants had persistent colic symptoms at 3 months of age.4 For breastfed infants with colic, episodes of distress are usually clustered in the late evening and early morning hours,5,6 which may cause significant disruption of family interactions7,8 and may lead to maternal exhaustion and distress.9 Colic is also associated frequently with secondary feeding difficulties.10 Generally, colic is thought to represent a transient, nonorganic, behavior dysregulation among otherwise healthy infants.9,11 However, the cause of infantile colic has remained unclear.2,9,11,12 Several psychosocial factors and maternal smoking have been shown to increase the risk of infantile colic.13,14

The role of diet in infantile colic is controversial.5 Among formula-fed infants with colic, use of extensively hydrolyzed casein- and whey-based preparations is associated with significant improvement in colic symptoms.15,16 Breastfeeding does not seem to be protective against infantile colic.2 However, several studies reported a reduction in persistent crying after elimination of cow’s milk and other food proteins from the maternal diet.17,19 A systematic review examining studies on maternal diet modification and colic suggested a possible therapeutic benefit but findings remained inconclusive, mainly because of limitations in the studies included in the meta-analysis.20

In our previous colic study,19 the greatest treatment benefit of 1-week maternal food allergen elimination was observed among breastfed infants <6 weeks of age. The statistical power in that study, however, was insufficient for drawing firm conclusions. In the present trial, we tested prospectively the significance of the findings; we evaluated the effect of a hypoallergenic maternal elimination diet on persistent crying among breastfed infants presenting with colic in this age group.

METHODS

Study Design

We performed a randomized, controlled trial to test the hypothesis that, among breastfed infants with colic presenting in the first 6 weeks of life, elimination of multiple, major, allergenic food proteins from the maternal diet is associated with a reduction in crying and fussing. The trial compared infants’ cry/fuss duration
before and 1 week after implementation of a low-allergen maternal elimination diet. The study was approved by the Ethics in Human Research Committee at the Royal Children’s Hospital, and written informed consent was obtained from the parents before randomization.

Recruitment
Between 2000 and 2002, exclusively breastfed infants <6 weeks of age with colic were recruited from metropolitan, community-based, well-infant centers in Melbourne, Australia. The recruitment phase was conducted by a lactation consultant (B.S.), who had no access to the randomization schedule. Only well, term infants (gestational age of >37 weeks) who were the result of a normal singleton pregnancy and who had an otherwise uneventful perinatal history (ie, no significant obstetric complications or history of maternal substance use) and no perinatal morbidity other than distress (ie, no perinatal asphyxia or perinatal infection) were enrolled.

Mothers were told the study was comparing the effects of 2 different diet programs that had been found previously to be of benefit in the treatment of infantile colic.38 Mothers on strict vegan diets were excluded from randomized treatment; 3 mothers on balanced ovo-lacto-vegetarian diets were included in the study.

Baseline Assessment
After recruitment, all infants underwent a detailed physical examination performed by a consultant neonatologist (N.R. or J.S.), and satisfactory breastfeeding technique was confirmed by a lactation consultant (B.S.) at the Royal Women's Hospital. A questionnaire to document sociodemographic data was administered. Mothers also were asked to keep a detailed food diary while maintaining their usual diet before and 1 week after implementation of a low-allergen maternal elimination diet. The study was approved by the Ethics in Human Research Committee at the Royal Children’s Hospital, and written informed consent was obtained from the parents before randomization.

Interventions
The effects of 2 maternal diet programs, ie, a low-allergen diet that excluded major food allergens and a control diet that included these foods, were compared. Both diets avoided food preservatives, colors, and additives. Mothers were assigned to one of the diets by the research dietitian (D.E.F.), on the basis of a randomization schedule provided by the statistician (J.B.C.). The dietitian explained the diet and provided detailed written information but played no role in the collection or analysis of cry/fuss outcome data. The diet intervention commenced at 6 am on day 3 and continued until 6 am on day 10. Contact between the mothers was avoided to prevent contamination of information between the groups. All infants were breastfed exclusively for the duration of the study. The diet regimens were isonitrogenic and designed to provide adequate energy (1.16 MJ/day) and protein (protein 115 g/day) for breastfeeding mothers. Adherence to the diet was monitored with diet diaries maintained for 48 hours on days 8 and 9.

Low-Allergen Diet
For the low-allergen diet, mothers were instructed to exclude all foods containing dairy products, soy, wheat, eggs, peanuts, tree nuts, and fish from their diet. Their diet included a rice milk drink, meats, vegetables, fruits, and cereals (corn and rice). A calcium supplement (1.2 g/day) was prescribed. Mothers were supplied with a rice-based drink in powder form (500 mL/day), as well as a daily supply of fresh rice bread.

Control Diet
The control diet included all of the food items excluded from the low-allergen diet. Mothers received 7 days of rations of a soy and cow’s milk powder mixture to make 500 mL of a milk drink per day (equivalent to 200 mL of soy milk and 300 mL of cow’s milk). Mothers were asked to eat 1 serving of peanuts, 1 serving of wheat, and 1 chocolate muesli bar per day, which were supplied. Mothers also were encouraged to maintain their usual intake of vegetables, meats, rice, and other cereals.

Outcomes
Cry/fuss charts were recorded by mothers for 48 hours starting at 6 am on day 1 of the study (baseline data, ie, days 1 and 2). Cry/fuss charts for outcome assessment were completed from 6 am on day 8 to 6 am on day 10 (outcome days 8 and 9). Cry/fuss charts were scored by the study nurse (J.B.) and an independent reviewer, both of whom were blinded to the diet allocations. For each 48-hour assessment period (days 1 and 2 or days 8 and 9), the total duration of crying/fussing was calculated independently by the 2 reviewers and the mean of the 2 assessments was used for analysis.

Table 1: Demographic Characteristics of Study Cohort and Infants Withdrawn Before Study Completion

<table>
<thead>
<tr>
<th></th>
<th>Completers</th>
<th>Noncompleters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-Allergen Diet</td>
<td>47</td>
<td>6</td>
</tr>
<tr>
<td>Control Diet</td>
<td>43</td>
<td>11</td>
</tr>
<tr>
<td>Low-Allergen Diet</td>
<td>47</td>
<td>6</td>
</tr>
<tr>
<td>Control Diet</td>
<td>43</td>
<td>11</td>
</tr>
</tbody>
</table>

Values are number (percentage) or mean (range).
The primary end point of the study was a reduction in cry/fuss duration of 25% between days 1 and 2 and days 8 and 9. Additional analyses were based on comparison of mean cry/fuss durations between groups. Analyses of the effects of diet were limited to infants for whom colic reportedly exceeded 3 hours/day for 3 days/week and had persisted for 3 weeks, according to the criteria described by Wessel et al.22 A final analysis was restricted to dyads for which complete adherence to the assigned diet was demonstrated.

Secondary outcomes involved maternal assessment of the infant’s response to maternal diet change. On the morning of day 10, the research nurse (J.B.) asked mothers to categorize their infant’s colic behavior as better, same, or worse. In addition, mothers graded their infant’s level of distress on a 10-cm visual analog scale (VAS) of 0 (no crying/fussing) to 10 (maximal crying/fussing). Measurements were read to the closest 0.5-cm marking.

Statistical Analyses

The primary analysis (intention-to-treat) compared the response rates between the 2 groups. We report the estimated difference in proportions with a standard 95% confidence interval and $\chi^2$ test. The distribution of cry/fuss duration was skewed positively; therefore, we used logarithmically transformed values for analysis and reported geometric means as summaries, with ratios for comparison between groups. Analyses of the continuous cry/fuss data used analysis of covariance (with logarithmic values) to compare the cry/fuss duration between groups (expressed in relative terms, as the geometric mean ratio), with adjustment for group differences in baseline crying duration.

Maternal assessment categories (better, same, and worse) were compared between treatment groups with $\chi^2$ analysis. The mean VAS score was calculated for each group, and values were compared with a 2-sample $t$ test.

RESULTS

Study Groups

Recruitment, reasons for noncompletion, and study progress are detailed in Fig 1. Of the 107 infants who entered this study, 90 (84%) completed the randomized trial (mean age at the time of diet allocation: 5.7 ± 1.1 weeks; range: 2.9–8.6 weeks; 54 male infants). The completion rates were 47 (89%) of 53 for the low-allergen group and 43 (80%) of 54 for the control group ($\chi^2 = 1.64, P = .20$). The demographic characteristics of the study cohort (completers and noncompleters) are summarized in Table 1.

![Fig 1. Diagram of patient enrollment and study progress.](http://pediatrics.aappublications.org/cgi/doi/10.1542/peds.2005-0147)
Primary Outcome

On the basis of a reduction in cry/fuss duration of ≥25%, 35 (74%) of 47 infants responded to the low-allergen diet group, compared with 16 (37%) of 43 infants on the control diet, ie, an absolute risk reduction of 37% (95% confidence interval: 18–56%; P < .001) (Table 2). Changing the cutoff value to 20% or 30% did not alter these results substantially (Table 3).

If all noncompleters were analyzed as nonresponders, then there was a 36% risk reduction for the low-allergen diet (P < .001) (Table 4). At the end of the study, 61 of 90 infants still had colic, ie, cry/fuss duration of ≥360 minutes per 48 hours (low-allergen group: 30 of 47 infants; control group: 31 of 43 infants; χ² = 0.70, P = .40). Figure 2 plots the individual data for the study participants.

Table 2 summarizes mean cry/fuss durations and assesses between-group differences. There was a small average difference in cry/fuss duration between the 2 arms of the study at baseline, before commencement of the diet (days 1 and 2). At the end of the study, however, the cry/fuss duration per 48 hours was reduced by a substantially greater amount in the low-allergen group; the adjusted geometric mean ratio was 0.79 (95% confidence interval: 0.63–0.97; P = .028), ie, an average reduction of 21% (95% confidence interval: 3–37%). This corresponds to reductions in adjusted geometric mean of distress levels of 40% (274 minutes per 48 hours) in the low-allergen group and 16% (102 minutes per 48 hours) in the control group (Table 2).

Of the 90 mother-infant dyads that completed the study, 80 (89%) fulfilled the definition of colic provided by Wessel et al.22 (≥3 hours of distress, on 3 days/week, for ≥3 weeks). Of these, 41 were assigned to the low-allergen diet and 39 to the control diet. Results were very similar in this subgroup, compared with the entire study cohort. In primary outcome analysis, 31 (76%) of 41 responded to the low-allergen diet, compared with 16 of 39 (41%) responding to the control diet (P = .002).

Secondary Outcomes

The categorical and VAS assessments were completed by 42 (89%) of 47 mothers in the low-allergen group and by 39 (91%) of 43 in the control group. There were no significant differences in the maternal categorical assessments of treatment responses (better, same, or worse) or continuous assessments with the VAS on day 10 between the 2 diet groups (Table 2).

Adherence to Diet Programs

At baseline (days 1 and 2), complete diaries were available for 87 of 90 patients (low-allergen diet: 46 of 47 patients; control diet: 41 of 43 patients). Before the study, there were only minor differences in diet between the groups. Patients assigned randomly to the control diet had a higher intake of wheat protein (mean intake: 31.2 g per 48 hours vs 26.2 g per 48 hours; P < .05), whereas the intake of peanut protein was higher in the group assigned to the low-allergen diet (mean intake: 2.0 g per 48 hours vs 0.9 g per 48 hours; P = .05). Intakes of milk, eggs, and chocolate were similar for the 2 groups at baseline.

At completion of the study (days 8 and 9), interpretable diet diary records were available for 45 (96%) of 47 patients on the low-allergen diet and 41 (95%) of 43 control patients. In the low-allergen group, 44 (98%) of 45 mothers were deemed compliant with the diet and had avoided all wheat, dairy, eggs, peanuts, and chocolate successfully; 1 noncompliant mother (identification number 93, responder) had eliminated milk, eggs, and chocolate but had continued to ingest wheat (23 g of wheat protein per 48 hours) and peanut (6.8 g of peanut protein per 48 hours). In the control diet group, complete diet adherence was achieved by 24 (59%) of 41 patients; the remaining 17 (41%) of 41 patients were partially compliant and had eliminated up to 3 food items on days 8 and 9. All had continued to ingest wheat, and none had commenced the full low-allergen diet. For the control diet group, the median protein intakes were

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**TABLE 2. Rate of Response to Treatment and Change in Cry/Fuss Scores at Baseline (Days 1 and 2) and Follow-Up (Days 8 and 9)***

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Low-Allergen Diet</th>
<th>Control Diet</th>
<th>Difference, % (Mean), or Ratio (Geometric Mean)</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Categorical analysis, no. (%) Improvement of ≥25% (days 1 and 2 versus days 8 and 9)</td>
<td>35 of 47 (74)</td>
<td>16 of 43 (37)</td>
<td>37</td>
<td>18–56</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cry/fuss duration of ≥360 min per 48 h (days 8 and 9)</td>
<td>30 of 47 (64)</td>
<td>31 of 43 (72)</td>
<td>8</td>
<td>−11–27</td>
<td>.402</td>
</tr>
<tr>
<td>Continuous analysis, min per 48 h (geometric mean and 1-SD range)</td>
<td>690 (498–963)</td>
<td>631 (433–925)</td>
<td>1.1</td>
<td>0.66–1.08</td>
<td>.18</td>
</tr>
<tr>
<td>Days 1 and 2</td>
<td>431 (252–742)</td>
<td>509 (270–953)</td>
<td>0.85</td>
<td>0.63–0.97</td>
<td>.028</td>
</tr>
<tr>
<td>Days 8 and 9 adjusted*</td>
<td>416</td>
<td>529</td>
<td>0.79</td>
<td>0.63–0.97</td>
<td>.028</td>
</tr>
<tr>
<td>Secondary outcomes VAS score (mean ± SD) Maternal categories, no.</td>
<td>4.3 ± 2.5</td>
<td>5.0 ± 2.8</td>
<td>0.7</td>
<td>−0.43–1.87</td>
<td>.218</td>
</tr>
<tr>
<td>Better</td>
<td>29</td>
<td>22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Same</td>
<td>8</td>
<td>9</td>
<td></td>
<td></td>
<td>.45</td>
</tr>
<tr>
<td>Worse</td>
<td>5</td>
<td>8</td>
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</table>

*Comparison adjusted for baseline differences with analysis of covariance.
31 g of wheat, 39 g of cow’s milk, 6 g of eggs, 6 g of peanuts, and 7.6 g of chocolate per 48 hours.

There were 41 control group dyads with interpretable diet diaries, including 16 (39%) responders and 25 (61%) nonresponders. Of the 16 control group responders, 14 (88%) had adhered strictly to the diet, whereas only 10 (40%) of 25 nonresponders were deemed compliant. The remaining 15 mothers who had failed to respond to the control diet had subsequently removed food allergens from their diet, including the milk/soy drink (n = 4), eggs (n = 11), peanuts (n = 6), and chocolate (n = 4). Therefore, mothers of nonresponders in the control group were significantly more likely to breach the diet protocol than were those of responders (rate of noncompliance in the control group: 2 of 16 responders vs 15 of 25 nonresponders; χ² = 7.22, P = .007). When the primary outcome analysis was restricted to dyads that adhered fully to the assigned diet on days 8 and 9, as documented by dietary records, 33 (75%) of 44 responded in the low-allergen group, compared with 14 of 24 (58%) in the control group (χ² = 2.02, P = .15).

**DISCUSSION**

The present study demonstrated that elimination of several major food allergens from the diet of breastfeeding mothers for 1 week was associated with a significant reduction in their infant’s cry/fuss duration. The primary outcome analysis, based on
The current study was designed to test prospectively whether the dietary programs, the apparent treatment benefit for the low-allergen group was reduced. However, this analysis is difficult to interpret because noncompliance in the control arm was associated with a lack of early response to diet. This might have resulted in a form of reverse causation (ie, a lack of early response to diet increased the risk of noncompliance and thus biased the remaining compliant control dyads toward a better treatment outcome).

The self-limiting nature of colic has precluded the use of invasive investigations to establish a pathophysiologic model of infantile colic. The mechanisms through which maternally ingested food proteins elicit colic symptoms among breastfed infants thus remain speculative. Cow’s milk,26 egg,27 peanut,28 and wheat29 antigens have been detected in human milk and may evoke gastrointestinal mucosal immune responses.30 Mucosal IgE-containing plasma cells were increased in upper jejunal biopsies from infants with cow’s milk-induced colic.31 Previous studies demonstrated that macromolecular gut permeability is increased among infants with colic, which may predispose these infants to food sensitization,32,33 as well as gastrointestinal34 and cutaneous33 manifestations of food allergies during early childhood. Infants with colic also show abnormalities in gastrointestinal hormones and regulatory intestinal peptides, including cholecystokinin and motilin.35,36 The effects of reduced cholecystokinin levels in colic are poorly understood but may involve impaired central regulation of satiety and behavior.36 The finding of increased serum motilin levels among infants with colic provides indirect evidence of altered gut motility for these infants.35 Motilin, a regulatory gut polypeptide, is the main stimulant for interdigestive migrating gut contractions.37 We speculate that these propulsive gut contractions may cause visceral pain and trigger episodes of distress. Motilin has been found in human milk38 and may trigger endogenous release of motilin among breastfed infants.39 There is some evidence that maternal smoking, a recognized risk factor for colic, may cause gastrointestinal motility disturbances through increased plasma and intestinal motilin levels.40 The effects of motilin are inhibited by atropine, which may explain why atropine and similar anticholinergic compounds ameliorate colic symptoms.41,42 It is unclear whether food proteins are able to stimulate endogenous motilin secretion either directly or indirectly, through immune-mediated mechanisms.

This study is the first randomized, controlled trial to demonstrate a clear effect of maternally ingested food proteins on colic symptoms among breastfed infants. Our observations were based on a representative, community-based sample of infants with colic, with age and clinical characteristics similar to those in previous interventional studies of colic.15–19 The study had several limitations. Because of the nature of the intervention, the study could not be conducted as a double-blind trial, although mothers in both diet groups had to make substantial changes to their diets. Therefore, the outcomes might have been affected by a placebo effect. Furthermore, challenges were not performed to demonstrate relapse of symptoms after reintroduction of food proteins into the maternal diet.

Our investigation was designed to provide proof of the concept and to test prospectively the observa-
tions from our previous study, rather than to evaluate the role of individual food proteins in infantile colic. However, it is acknowledged that factors other than diet may also be involved in the pathogenesis of infant distress. Elimination diets have associated risks, particularly if sustained for long periods, and the nutritional progress of the infant and the mother needs to be monitored closely by an experienced dietitian. Additional studies are needed to define the pathophysiological features and role of maternal elimination diets in infantile colic.

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REFERENCES

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