Fortifying Milk with Ferrous Gluconate and Zinc Oxide in a Public Nutrition Program Reduced the Prevalence of Anemia in Toddlers[1]

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Abstract

We aimed to assess the efficacy of whole cow's milk fortified with ferrous gluconate and zinc oxide, along with ascorbic acid, in reducing the prevalence of anemia and improving iron status of low income children 10–30 mo of age. Healthy children were randomly assigned to drink 400 mL/d of cow's whole milk, either fortified milk (FM) with 5.8 mg/400 mL of iron as ferrous gluconate, 5.28 mg/400 mL of zinc as zinc oxide, and 48 mg/400 mL of ascorbic acid, or nonfortified milk (NFM) with 0.2 mg iron/400 mL, 1.9 mg zinc/400 mL, and 6.8 mg ascorbic acid/400 mL. Hemoglobin, serum ferritin, soluble transferrin receptors (TfR), and C-reactive protein concentrations were measured at baseline and 6 mo after intervention. The prevalence of anemia declined from 41.4 to 12.1% ($P < 0.001$), or 29 percentage points, in the FM group; there was no change in the NFM group. Hemoglobin (coefficient = 0.22, $P < 0.01$) was positively and TfR (coefficient = −0.29, $P < 0.001$) negatively associated with treatment, controlling for their respective baseline values, age, and gender. Treatment with FM was negatively associated with the likelihood of being anemic (pseudo $R^2 = 0.085$, $P < 0.03$) after 6 mo of intervention. Ferrous gluconate added to whole cow's milk as a fortificant along with ascorbic acid is efficacious in reducing the prevalence of anemia and in improving iron status of Mexican toddlers. The results of this study lead to broadening a subsidized FM distribution program to 4.2 million beneficiary children 1–11 y of age in Mexico. J. Nutr. 136: 2633–2637, 2006.

Introduction

The prevalence of iron deficiency anemia (IDA)[2] in Mexican children is high. A peak prevalence of 48% is found in infants 12–23 mo of age and it remains at ~20% during school age (1). For many decades, the Mexican government has sold whole milk at subsidized prices to low income households with children 1–11 y of age through a federal program (Liconsa). In 2000 a decision was made to fortify the subsidized milk with iron and other micronutrients to contribute to the reduction of IDA and other micronutrient deficiencies. At that time, ~4.2 million children 1–11 y old from low income families were beneficiaries of Liconsa. Although fortification of infant's formulas is a common practice globally, there are very few examples of interventions using iron-fortified whole milk in public nutrition programs (2). Inorganic iron compounds added to whole cow's milk are poorly absorbed (3), because the compounds attach extensively to whey proteins, casein micelles, salts, and fat droplets, reducing its solubility (4); however, organic compounds of iron (lactate and gluconate) absorb more easily to the water phase of milk (3-fold solubility in milk water phase, relative to ferrous sulfate) (4). Addition of ascorbic acid to milk improves the net iron absorption from ferrous sulfate by up to 10%, making milk a suitable vehicle for a fortification program (5,6). The water solubility of ferrous gluconate, it has been reported to have a similar absorption to ferrous sulfate in both rats and humans (7). There is no information in the literature of any previous experience in the use of ferrous gluconate as milk fortificant in large-scale nutrition interventions.

This investigation was designed to assess the efficacy of the fortification of powdered cow's milk with ferrous gluconate, in combination with ascorbic acid, in reducing the prevalence of IDA in a sample of Mexican toddlers with a high prevalence of anemia. We expected that the results of this trial would be useful for decision making regarding broadening the program nationwide.

Population and Methods

This randomized clinical trial was carried out in a poor periurban community of 5000 inhabitants in the outskirts of Puebla, a city located 120 km east of Mexico City. Healthy children 10–30 mo of age at the beginning of the study were selected from a registry of children younger than 5 y of age living in the community. Such a registry is maintained and periodically updated by the local health facility. Parents or legal guardians signed an informed consent letter after a careful explanation of the objectives, nature, and risks of the study. The protocol was reviewed and approved by the Research, Ethics and Biohazards Committees from the National Public Health Institute, Cuernavaca, Mexico.

Children were randomly assigned to drink 400 mL/d (200 mL in the morning, 200 mL in the evening) of cow's whole milk (distributed as

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[2] Abbreviations used: CRP, C-reactive protein; FM, fortified milk; IDA, iron deficiency anemia; NFM, nonfortified milk; PP, percent points; TfR, soluble transferrin receptors.

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milk powder) either fortified (FM) with 5.28 mg/400 mL of iron as ferrous gluconate and other micronutrients or nonfortified milk (NFM) (iron concentration: 0.2 mg/400 mL). FM was supplemented with ferrous gluconate, zinc oxide, sodium ascorbate, and folic acid, as described in **Table 1**. The micronutrient premix, purchased from DSM Nutritional Products, was added to the powdered milk in the plant by the manufacturer (Liconsa) using an electronic dispenser and a sifter. Units of 220 g of the product were packed in metallic foil sachets. The packages of FM and NFM were undistinguishable, except for a color-coded band in the upper corner of the sachet. The color code was unknown to researchers, field workers, and users and was disclosed after data analysis.

Mothers or caregivers of infants were instructed how to reconstitute the powdered milk, which was delivered weekly to each family, and about the amount of milk intended for the infant to drink daily. A field worker visited the household 2 times/d, at the usual times of milk intake by the child, to verify the correct reconstitution of milk and to register the amount of milk consumed. When mothers offered extra milk to their children or when children were not at home at the time of the visit, mothers were asked the following day to estimate the amount of milk drunk by the child.

Blood samples. Hemoglobin concentration was determined in capillary blood samples obtained by finger prick and measured in a Portable Photometer Hemocue (HemoCue) (8,9). Variability of photometers was assessed during fieldwork at the beginning and at the end of each working day. We used a 3-level liquid quality control check (4C-ESControl, Beckman-Coulter) and the readings of a precalibrated reference cuvette, included with the equipment. The mean difference between duplicates was 0.3 ± 9.9 g/L ($P = 0.36$ for liquid quality control material and −0.24 ± 3.6 g/L, $P = 0.27$ for the reference cuvette).

Venous blood samples were drawn from an antecubital vein at baseline and 6 mo after the initiation of the intervention. Samples were centrifuged at 268 × *g*; 20 min in situ and serum was stored in color-coded cryovials in liquid nitrogen until delivery to a central laboratory. Commercial kits were used to measure the serum concentrations of ferritin (Dade Behring), soluble transferrin receptors (TfR) (Dade Behring) by ELISA, and C-reactive protein (CRP) by nephelometry, using monoclonal antibodies (Behring Nephelometer 100 Analyzer, Behring Laboratories). Serum zinc was measured by atomic absorption spectrometry using a spectrometer Analyst 300 (Perkin-Elmer). In our laboratory, standard reference material 3168a from NIST (U.S. Department of Commerce) at a concentration of 1 mg/L had a 2.3% CV.

Operative definitions of anemia and iron deficiency. Anemia was defined according to WHO recommendations as hemoglobin concentrations <110 g/L at sea level (10). Hemoglobin concentrations were adjusted for altitude following the equation proposed by Cohen and Haas (11). Iron deficiency was defined as serum ferritin concentration <12 μg/L and TfR >6 mg/L.

Sample size calculations and statistical analysis. The minimum sample size was calculated using the following assumptions: a Δ of 10 percent points (PP) in the prevalence of anemia, an α-value of 0.05 and a β of 0.8, this resulted in a sample size of 77 children/treatment group.

Unadjusted comparisons between means were done using ANOVA and Bonferroni's test as the post hoc test, and between proportions using chi-square tests, and a Wilcoxon's Signed Rank test. Effects of treatment were assessed by linear regression models in which final concentrations of hemoglobin, serum log-ferritin, TfR, and zinc were alternately used as dependent variables. Treatment, age, gender, body wt, and baseline hemoglobin, log-ferritin, TfR, or zinc concentrations, when appropriate, were used as independent variables. Also, CRP concentrations at 6 mo were introduced into the models analyzing log-ferritin and zinc. A logistic regression model was constructed with final anemia as the dependent variable and age, gender, treatment, and baseline anemia as independent variables. Serum ferritin data were not normally distributed; thus, they were transformed logarithmically for statistical analysis. Ferritin values are expressed throughout the text as antilogarithms. Statistical analyses were performed with the statistical software Stata, V. 7.2 for Windows, (Stata, 2001). Values in the text are means ± SD, unless otherwise indicated.

Results

Characteristics of the sample. For the present analysis, a final sample of 115 children (NFM = 57, FM = 58) was assembled (**Fig. 1**). Age, wt, length, energy intake, and distribution by gender did not differ between groups at baseline or at 6 mo (**Table 2**). Most of the children (93%) were breast-fed, with a mean duration of 12 mo; by 4 mo of age, most of them received nonnutritive liquids. Solid foods were introduced at 6 mo of age. These variables did not differ between the groups (data not shown). Most of the households belonged to a low socioeconomic level, as shown by the frequency of cement floor, pipe water and toilet availability, and possessions (Table 2). Compliance was 86%; that is, children drank the planned amount of milk 6 out of 7 d of the week and the 2 groups did not differ. A field worker observed and registered milk intake in 96% of the planned observation days. The daily intake of milk, calculated from the daily intake for the entire 6-mo period, was 529 ± 201 mL for the FM group and 482 ± 178 mL for NFM group ($P > 0.05$). The initial total intake of dietary iron did not differ between FM and NFM groups (5.58 ± 6.3 vs. 5.26 ± 5.16 mg/d, $P < 0.3$), but the final total intake was higher in the FM group (15.7 ± 13.4 g/d) than in the NFM group (6.4 ± 5.1 mg/d, $P < 0.04$).

Hemoglobin and the prevalence of anemia. The unadjusted concentrations of hemoglobin increased after 6 mo of intervention in the group treated with FM (118.3 ± 13.5 and 127.4 ± 11.5 g/L at baseline and at 6 mo, respectively, $P < 0.01$), but not in the NFM group (124.1 ± 14.4 and 124.0 ± 12.4 g/L, respectively). At 6 mo, the concentration was greater in the FM group than in the NFM group ($P < 0.05$).

TABLE 1 Proximate composition of powdered milk and amounts of micronutrients added to the FM

	FM		NFM	
	Unit/kg dry powder	Unit/400 mL reconstituted milk[1]	Unit/kg dry powder	Unit/400 mL reconstituted milk
Energy, *kJ*	20680	992	20680	992
Protein, *g*	259	12.5	259	12.5
Fat, *g*	259	12.5	259	12.5
Carbohydrates, *g*	389	18.7	389	18.7
Iron (ferrous gluconate), *mg*	109.8	5.28	4.1	0.2
Zinc (zinc oxide), *mg*	109.8	5.28	41.6	1.9
Retinol palmitate, *μg*	449	21.6	449	21.6
Vitamin C (sodium ascorbate), *mg*	998	48	141	6.8
Folic acid, *μg*	669	32.1	110	5.2

[1] Powdered milk (48 g) in 400 mL of water.

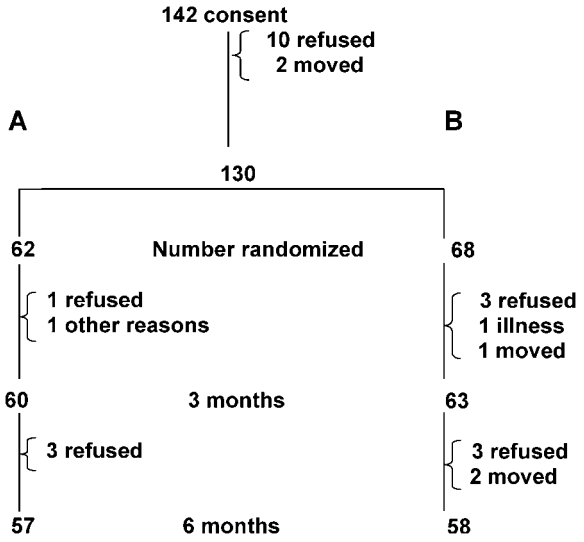

Figure 1 Profile of children in the supplementation trial at recruitment, randomization, and the reasons for losses to follow-up at different stages of the trial, by treatment group; A = NFM; B = FM group.

The unadjusted prevalence of anemia of the group that consumed FM declined from 41.4 to 12.1% ($P < 0.001$), or 29 PP, whereas there was no change in NFM group (30% and 24% at baseline and 6 mo, respectively; $P = 0.40$). The proportion of the change in the FM group that was attributable to the intervention was 24 PP (Δ of basal-6 mo prevalence for the FM group, minus Δ of basal-6 mo prevalence for the NFM group), representing a 58% reduction from the baseline prevalence of anemia in the fortified group. To further clarify this effect, we performed a Wilcoxon's Signed Rank test, which substantiated the significant effect (ties, 49 vs. 54, "positive" differences 29 vs. 16, negative differences 3 vs. 9, in FM and NFM subjects, respectively, $P < 0.001$). In a linear regression model, hemoglobin concentrations were positively associated with treatment FM (standardized coefficient = 0.22, $P < 0.01$), controlling for baseline hemoglobin, body wt and height, and by age and gender. The adjusted mean hemoglobin concentration in the FM was higher than in the NFM group ($P = 0.001$) (**Table 3**). In a multiple linear logistic regression model, with final anemia as the dependent variable (adjusted hemoglobin < 110 g/L), treatment with FM ($P < 0.03$) was negatively associated with the likelihood of being anemic after 6 mo of intervention, controlling for age, gender, and baseline anemia (**Table 4**).

Iron status. The unadjusted baseline concentrations of ferritin increased in the group treated with FM from 6.79 (95% CI 3.4, 10.1) to 13.1 (95% CI 10.8, 15.5) μg/L ($P < 0.001$) but not in the NFM group (baseline = 9.52, 95% CI 5.3, 13.6; 6 mo = 28.4, CI 7.9, 15.6 μg/L, $P = 0.06$). The groups did not differ at 6 mo ($P = 0.7$). The changes between baseline and 6 mo did not differ between the FM group (Δ = 5.52 ± 6.6 pmol/L) and the NFM group (Δ =3.41 ± 7.9 pmol/L, $P < 0.06$). The serum soluble TfR decreased significantly after 6 mo of intervention in both the FM group (from 6.04 ± 3.16 to 4.4 ± 1.15 mg/L, respectively, $P < 0.001$) and the NFM group (from 5.56 ± 2.24 to 5.01 ± 1.96 mg/L, $P < 0.01$). After 6 mo of intervention, the TfR concentrations did not differ between groups ($P = 0.09$). A reduction in the prevalence of iron deficiency, as indicated by ferritin <12 μg/L, occurred in the FM group from 66.7 to 28.3% ($P < 0.001$), or 38 PP. The proportion of the change in the FM group that was attributable to the intervention was 22 PP, representing a 36% reduction in the prevalence of iron deficiency in the fortified group. The prevalence of iron deficiency, as indicated by TfR >6 mg/L, decreased in the FM group from 54.2 to 28.2% ($P < 0.001$) but not in the NFM group (41.3 and 44.7% at baseline and 6 mo, respectively; $P = 0.30$). The proportion of this change in the FM group that was attributable to the intervention was 29 PP, representing a 53% reduction in the prevalence of iron deficiency in the fortified group.

Two linear regression models were constructed; 1 used 6 mo log-ferritin and the second 6 mo TfR concentrations as dependent variables. Covariables were baseline log-ferritin or TfR, when appropriate, as well as treatment (NFM = 0, FM = 1), 6 mo CRP concentration, age, gender, body wt, and height. The treatment did not affect log-ferritin concentration at 6 mo ($P = 0.08$). In contrast, serum TfR concentrations were negatively associated with FM treatment (standardized coefficient = 0.29, $P < 0.001$). The adjusted mean serum TfR concentration was lower in the FM than in the NFM group ($P = 0.001$) (Table 3).

TABLE 2 Selected characteristics of the study subjects and households at the randomization stage[1]

Variables	NFM, $n = 62$	FM, $n = 68$
Age, *mo*	22.5 ± 8.6	20.4 ± 4.9
Body weight, *kg*	10.9 ± 2.18	10.8 ± 1.6
Length, *cm*	80.7 ± 7.6	79.9 ± 5.1
Gender, *% females*	50.9	48.3
Milk intake, *g/d*	529 ± 201	482 ± 178
Compliance,[2] *%*	84.7 ± 2.4	88.3 ± 2.4
Energy intake, *kJ/d*	3817 ± 1041	3882 ± 1025
Household characteristics, *%*		
Cement floor	76.9	79.3
Pipe water in-house	31.9	26.4
Pipe water at the house's door	58.6	52.7
Toilet	90.1	83.9
Household assets, *%*		
TV set	97.8	98.9
Gas stove	95.6	96.6
Refrigerator	58.2	55.2

[1] Values are means ± SD or %; groups did not differ in any variable.
[2] Percent of days drinking milk/observed days.

TABLE 3 Final adjusted mean hemoglobin, serum log-ferritin, soluble transferrin receptor, and zinc concentrations of children treated with FM or NFM[1]

	NFM, $n = 57$	FM, $n = 58$
Hemoglobin, *g/L*	124.1 ± 0.59	127.4 ± 0.5*
Log-Ferritin[2], *μg/L*	11.43 (2.97, 42.6)	11.35 (3.69, 38.6)
Soluble transferrin receptors, *mg/L*	5.16 ± 1.02	4.5 ± 1.16*
Zinc[3], *μmol/L*	13.07 ± 1.0	12.61 ± 0.96

[1] Values are adjusted means ± SD unless noted otherwise from linear regression models controlled for baseline hemoglobin, serum log-ferritin, TfR, or zinc, when appropriate, age, gender, body wt and height; log-ferritin and zinc regression models were also adjusted by CRP. Symbols indicate different from NFM group: *Different from NFM, $P > 0.001$.
[2] Values are the antilog of original log-ferritin values (95% CI).
[3] To convert serum zinc to μg/dL, multiply by 6.53.

TABLE 4 The effect of FM on the final prevalence of anemia assessed by a multiple logistic regression model[1]

Variable	Coefficient	*P*
Treatment[2]	−0.86	0.03
Age, *mo*	−0.13	0.75
Baseline anemia	1.38	0.001
Gender [3]	−0.82	0.62

[1] $n = 115$, pseudo $R^2 = 0.085$.
[2] Fortified = 1, nonfortified = 0.
[3] Male = 1, female = 0.

The adjusted mean serum zinc concentration did not differ between the groups ($P = 0.3$) (Table 3).

Discussion

We present here evidence that fortification of powdered whole cow's milk with ferrous gluconate and zinc oxide in combination with ascorbic acid is efficacious in reducing the prevalence of anemia and improving iron status indicators in a sample of infants 10–30 mo of age. Published efficacy evaluations of interventions using fortified whole cow's milk have reported varying degrees of success (6,12–15). A study of 276 Chilean children, 3 mo old at the beginning of the intervention, were treated for 12 mo with cow's milk fortified with 15 mg/L of iron as ferrous sulfate (6). This study reported a dramatic reduction in the prevalence of anemia to 2.5% and of abnormal serum ferritin concentration to 8.5% in the group treated with fortified milk, compared with 25.7% and 39%, respectively, of a group treated with unfortified milk. Two further studies of Chilean infants (14,15) confirmed the efficacy of the fortification of milk with ferrous sulfate combined with ascorbic acid. In another study, 185 Brazilian children with mild or severe anemia were treated for 222 d with cow's whole milk fortified with 3 mg/L of aminochelate iron (12). After 222 d of intervention, 43% remained anemic. The low efficacy in this study was related to the low level of iron fortification (3 mg/L). A controlled trial in 36 Swedish children treated for 6 mo with cow's milk unfortified or fortified with 7.0 or 14.9 mg/L of iron reported no significant effects on hematological and iron status indicators (13). These children had a good baseline iron status from the beginning; thus, noticeable changes in hemoglobin or iron status should not be expected. We were unable to find any published report using ferrous gluconate as a fortificant for nutritional interventions.

Although ferrous sulfate along with vitamin C added to powdered cow's whole milk proved to be effective in reducing the prevalence of anemia in other studies (5,6), ferrous gluconate caused less organoleptic alterations to the milk when tested by the manufacturers of the milk used in this study (our unpublished data). Based on this evidence and the assumption of a similar bioavailability between ferrous sulfate and gluconate (7), the latter was selected as the fortificant to be tested in this efficacy study. The strengths of the present study are its design as a randomized, double blinded clinical trial, and the control for the secular improvement in iron status and in the prevalence of anemia, observed frequently in this age group. One limitation of our study is that the randomization procedure did not result in an even distribution of baseline anemia in the 2 intervention groups (30.0% NFM, 41.4% FM). Theoretically, such a difference made the FM group more susceptible to a larger improvement. The marked reduction in the prevalence of anemia (29 PP) in the prevalence of iron deficiency in FM group, compared with the modest decrease in the NFM group (6 PP) supports a specific effect attributable to the intervention. The strongest evidence for the effect of milk fortification lies in the lineal regression models where the treatment with FM was positively associated with hemoglobin and negatively with TfR concentrations, respectively, adjusting for baseline values of the dependent variables and other covariates. In the logistic regression model, treatment with FM was negatively associated with the likelihood of having anemia after the intervention, controlling for baseline anemia, age, and gender. The lack of a significant effect of treatment on the serum ferritin concentrations may be explained by: a) lack of power to detect differences, because sample size calculations were based on the prevalence of anemia; or b) the confounding effect of the frequently elevated CRP values (FM group, 17.5%, $n = 10$ and NFM group, 20.8%, $n = 13$). However, no changes in the overall results were observed when ferritin values of CRP positive subjects were excluded from the nonadjusted and adjusted analysis.

It is worthwhile to emphasize that milk was fortified with iron and zinc at a molar ratio 1.2, Fe:Zn. Thus, the effects on the prevalence of anemia and iron status herein described were most probably modulated by the interaction of both cations at the intestinal level, resulting in a lower efficacy in improving iron or zinc status than supplementation with either iron and zinc alone (16,17).

In summary, ferrous gluconate added as fortificant to cow's whole milk, along with ascorbic acid, is efficacious in reducing the prevalence of anemia and improving the iron status of Mexican preschoolers with a high prevalence of IDA. The results of this study led to the decision to scale-up an FM distribution program to 4.2 million beneficiary, low-income children, 1–11 y old in Mexico. Targeted beneficiaries are from families categorized in the food poverty range. This is an example of how the use of research can directly benefit the design of successful public nutrition programs.

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