Impact of Multiple Micronutrient Supplementation ("Sprinkles") on Iron Deficiency Anemia in Bedouin Arab and Jewish Infants

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ABSTRACT: **Background:** A high prevalence of iron deficiency anemia persists in Bedouin Arab and Jewish pediatric populations in southern Israel.

Objectives: To compare the effect of daily use of the micronutrient supplementation (MMS), "Sprinkles," a powdered formulation of iron, vitamins A and C, folic acid and zinc, with liquid iron and vitamins A and D on iron deficiency at 12 months of age.

Methods: The 621 eligible Bedouin and Jewish infants in the study were assigned to the MMS and control arms and received supplementations from age 6 to 12 months. We examined the change in hemoglobin, hematocrit, mean cell volume, red blood cell distribution, serum ferritin and transferrin saturation. In addition, we used the high Iron Deficiency Index (IDI) if two or more of the above six parameters showed abnormal levels.

Results: Rates of anemia decreased significantly over the 6 month period, from 58.8% to 40.6% among Bedouin infants ($P = 0.037$) and from 40.6 to 15.8% among Jewish infants ($P = 0.017$). In Bedouin infants the prevalence of high IDI decreased significantly from 79.2% to 67.4% ($P = 0.010$) in the MMS group, but there was no change in the controls. Among Jewish infants, the high IDI prevalence decreased from 67% to 55.6% with no statistically significant difference in the two study arms. In the multivariate analysis in Bedouin infants MMS use was associated with a reduced risk of 67% in high IDI at age 12 months as compared to controls ($P = 0.001$). Fewer side effects in the intervention groups in both ethnic populations were reported.

Conclusions: MMS fortification of home food can be recommended as an effective and safe method for preventing iron deficiency anemia at 12 months of age.

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KEY WORDS: infants, iron deficiency, anemia, multiple micronutrient supplementations (MMS), Sprinkles®

Iron deficiency anemia affects millions of children worldwide [1] and is associated with physical and cognitive delays [2]. Given the detrimental long-term effects of iron deficiency [1,2], its primary prevention in early childhood is a crucial public health issue.

In the last decade it was found that a novel powdered supplementation formulation, called "Sprinkles," in single-serve iron-containing sachets for daily home-food fortification is an appropriate strategy to improve the iron status in infants [3,4]. This multiple micronutrient supplementation was tested in severely anemic, malnourished, poor populations and was found to be an efficacious, easy-to-use and highly acceptable method for treating severe (< 9 g/dl) and moderate (< 10 g/dl) anemia [4-7]. A pooled analysis of studies on the efficacy of MMS in a variety of settings in Ghana, northern China, and Bangladesh showed that 55%–90% of the severely or moderately anemic infants who were provided with MMS became non-anemic (hemoglobin ≥ 10 g/dl) [3].

In southern Israel (the Negev), with the Bedouin Arab and Jewish populations differing in religion, culture, tradition and socioeconomic background, high rates of mild anemia (Hb < 11 g/dl) and low compliance with iron supplementation among infants and toddlers [8-11] persist despite recommendations for liquid iron supplementation from age 4 months.

Since MMS fortification was found to be efficacious for treatment of severe or moderate anemia and acceptable to parents in previous Israeli studies [8], we considered using this strategy for the prevention of iron deficiency anemia in infants at 12 months of age in southern Israel.

We performed a cluster randomized intervention trial to compare the efficacy of daily MMS home-food fortification with daily oral liquid supplementation of iron and vitamins A and D (the standard supplementation recommended by the Israel Ministry of Health at the time of the study). In this analysis, we present the efficacy of MMS in preventing anemia, iron deficiency at age 12 months and reported side effects, as compared to standard supplementation recommended from age 6 to 12 months.

MMS = multiple micronutrient supplementation
Hb = hemoglobin

SUBJECTS AND METHODS

The study was a controlled cluster randomized intervention trial, with Maternal and Child Health clinics, clusters, as the randomization unit, stratified by ethnic population groups. The overall study objectives and design have been described elsewhere [11]. Briefly, full-term healthy infants aged 5–7 months receiving food supplementation with or without breastfeeding were enrolled during the period July 2005–September 2007 in 12 neighborhood MCH clinics (there are 40 MCH clinics run by the Health Ministry in Negev settlements). At enrollment, a signed parental informed consent was obtained and personal interviews conducted, and blood tests of the infants were performed. During this encounter, a 1 month supply of supplementation (MMS or liquid formulation of iron and vitamins A and D) was provided.

The intervention was at the individual level in the MCH clinics. Participants in the intervention MMS arm (six clusters: two in Bedouin and four in Jewish settlements) were provided with free MMS sachets ("Sprinkles," Suppleforte™, Ped-Med Inc., Canada). Each sachet contained powder with 12.5 mg of elemental iron as microencapsulated ferrous fumarate, 5 mg zinc, 300 µg vitamin A, 7.5 µg vitamin D, 150 µg folic acid, and 50 mg ascorbic acid. The parents were instructed to add the powder to the infant's weaning food once daily. Participants in the standard supplementation arm, the control arm (six clusters: two in Bedouin and four in Jewish settlements) were supplied free of charge with bottles containing elemental iron as III hydroxide polymaltose complex, and vitamins A and D as a water-based formula. Parents were instructed on the daily administration of 6 iron drops (15 mg) and 2 drops of the vitamin A plus D formulation (300 µg vitamin A with 10 µg vitamin D). Both the study and control arms received their assigned monthly supplements at enrollment and subsequently at monthly visits for 6 months from enrollment. At these monthly visits a research assistant conducted a personal interview about feeding practices, use of supplementations, and morbidity and possible side effects of the interventions. In addition, the research assistant counted the remaining (unused) sachets and assessed the levels of liquids in the iron and vitamin A and D bottles. The researchers renewed supplies of supplements as needed and encouraged parents to continue their use. At enrollment and at age 12 months venous blood was drawn for hemoglobin, hematocrit, mean cell volume, red blood cell distribution, serum ferritin and transferrin saturation. At ages 6 and 12 months nutritional evaluation using a Short Food Frequency Questionnaire on iron intake was performed. All interviews were performed by trained interviewers speaking Arabic or Hebrew. We defined the following variables: anemia (Hb < 11 g/dl), low hematocrit (< 33%), low mean cell volume (< 77 fl), high RDW (> 14%), low serum ferritin (< 15 µg/L), low transferrin saturation (< 16%) (*Mortality and Morbidity Weekly Report*, Centers for Disease Control, 2002). Iron deficiency was defined by the Iron Deficiency Index as the presence of at least two abnormal findings from the above six iron deficiency indicators [12].

MCH = Maternal and Child Health
RDW = red blood cell distribution

STATISTICAL ANALYSIS

The paired *t*-test was used to examine the efficacy of the intervention at age 12 months. Linear regression analysis was used for controlling for baseline values of tested parameters within study groups. The differences in the proportion of children with abnormal iron deficiency indicators and IDI were compared between ages 6 and 12 months using the McNemar chi-square test. For variables with distribution other than normal, the non-parametric two-sample Kolmogorov-Smirnov test was used. The impact of the intervention on IDI at age 12 months, controlling for confounders and adjusting for clusters, was analyzed using multivariate conditional logistic regression (STATA 10). The study was approved by the Helsinki Committee of Soroka Medical Center and registered in the Clinical Trials Registry (Study NCT00276198).

RESULTS

At the completion of enrollment, the study population comprised 621 infants who had a first baseline blood test and whose parents had agreed to participate. There were 328 Bedouin infants from 4 clusters and 293 Jewish infants from an additional 8 clusters. Of the parents who received information about the study 88.5% gave their informed consent to participate. Infant mean age at enrollment was 6.0 ± 1.4 months. Among those enrolled, 450 completed the 6 month follow-up and had a second blood test at age 12 months; 254 (70.1%) were Bedouin and 196 (78.2%) were Jewish infants. There were no statistically significant differences in baseline socio-demographic characteristics between families who completed and those who did not complete the study, within each ethnic group.

We compared baseline socio-demographic characteristics and birth weight between the two study arms (MMS and controls) within each ethnic group and found no significant differences between the study arms in either ethnic group [Table 1]. However, there were significant differences in socio-demographic characteristics between ethnic groups. Bedouin parents were younger than their Jewish counterparts and had fewer years of education. The Bedouin families were significantly larger with a higher crowding index (persons per room) than Jewish families. There was no statistically significant difference in birth weight by ethnic group [Table 1].

We assessed iron consumption from food, as reported by parents, at enrollment at age 6 months and at age 12 months.

IDI = iron deficiency index

Table 1. Baseline characteristics of the study populations at enrollment (around age 6 months) by ethnic groups and study arms

	Bedouins			Jews		
	MMS (n=140)	Control (n=108)	*P*	MMS (n=97)	Control (n=99)	*P*
Gender, males, n (%)	74 (53.0)	59 (54.6)	0.76	53 (54.6)	52 (52.5)	0.60
Maternal education (yr), mean (SD)*	8.5 (4.1)	8.4 (3.9)	0.91	13.3 (1.9)	13.0 (2.0)	0.28
Paternal education (yr), mean (SD)*	9.4 (3.8)	9.9 (3.5)	0.26	12.8 (2.6)	12.7 (2.1)	0.26
Maternal age (yr), mean (SD)*	28.9 (6.5)	28.0 (6.6)	0.29	28.6 (5.0)	29.6 (5.9)	0.22
Paternal age (y)r, mean (SD)	30.9 (7.9)	32.9 (8.8)	0.14	32.8 (6.1)	32.4 (6.0)	0.91
No. of people in the family, mean (SD)*	6.3 (2.7)	6.2 (3.0)	0.76	4.6 (1.3)	5.0 (2.2)	0.09
No. of children < 5 yr in the family, mean (SD)*	2.4 (1.1)	2.3 (1.0)	0.48	1.6 (0.7)	1.5 (0.8)	0.48
No. of people in the family per room, mean (SD)*	2.4 (1.3)	2.2 (0.9)	0.51	1.3 (0.6)	1.3 (0.5)	0.50
Birth weight (g), mean (SD)	3127 (440)	3210 (478)	0.17	3273 (467)	3183 (564)	0.24

**P* for differences between Bedouin and Jewish children < 0.005

Table 2. Potential confounders by ethnic groups and study arms

	Bedouins			Jews		
	MMS	Control	*P*	MMS	Controls	*P*
Iron consumption from food before blood test at 6 months (mg/day)*	15.8 ± 17.1 (9.3)	14.2 ± 16.0 (7.7)	0.562	23.7 ± 21.5 (16.1)	20.0 ± 20.1 (10.1)	0.074
Iron consumption from food before blood test at 12 months (mg/day)*	26.8 ± 22.5 (19.3)	24.1 ± 19.6 (16.4)	0.972	28.1 ± 22.9 (23.1)	28.2 ± 26.9 (18.7)	0.939
Length of breastfeeding (mo)	6.6 ± 3.7 (6.6)	7.0 ± 3.6 (6.8)	0.756	6.6 ± 3.8 (6.5)	6.0 ± 3.4 (5.9)	0.202
Reported mean no. of days of supplementation use	149.1 ± 56.9 (140.0)	142.3 ± 54.3 (133.0)	0.985	141.1 ± 52.9 (158.0)	145.5 ± 55.5 (138.0)	0.827

Values are (means ± SD) with medians in parentheses (statistical significance of two-sample Kolmogorov-Smirnov tests)

* *P* for differences between Bedouin and Jewish children < 0.05

Jewish infants showed higher median dietary iron consumption than Bedouin infants, both at enrollment ($P < 0.001$) and at the end of follow-up ($P = 0.043$) [Table 2]. There were no statistically significant differences in reported dietary iron intake between intervention arms at both ages within ethnic groups. In addition, there were no differences in duration of breastfeeding between ethnic groups and between study arms within each ethnic group.

We examined the status of anemia and iron deficiency at baseline and found significantly higher rates of anemia and high IDI among Bedouin children as compared to Jewish infants. Overall, 58.8% of Bedouin and 40.6% of Jewish children had anemia at enrollment ($P = 0.016$), while 82.3% of Bedouin and 66.5% ($P = 0.019$) of Jewish infants had high IDI with no statistically significant differences between study arms within each ethnic group.

Table 3. Results from a multivariate conditional logistic regression analysis of the impact of MMS intervention on Iron Deficiency Index* at age 12 months, after controlling for a positive IDI value at age 6 months and clustering

	OR	95%CI	*P*
Bedouins			
Intervention group*	0.33	0.17–0.64	0.001
IDI at age 6 months	2.81	1.41–5.60	0.003
Jews			
Intervention group	1.2	0.71–2.32	0.402
IDI at age 6 months	1.8	1.77–6.14	< 0.001

*Intervention group = MMS vs. controls

High IDI (Iron Deficiency Index) = at least 2 of 6 iron deficiency indicators: hemoglobin < 11 g/dl, hematocrit < 32.9%, mean cell volume < 77 fl, red blood cell distribution > 14%, serum ferritin < 15 µg/L, transferrin saturation < 16%

The overall compliance with recommended supplementation was 145 of 180 days of potential use (80.6%). There was no statistically significant difference in compliance with supplementation by ethnic group, or between the study arms within two ethnic groups [Table 2]. We analyzed the efficacy of MMS intervention as the changes in anemia and iron deficiency rates over the 6 months of MMS intervention as compared to standard supplementation.

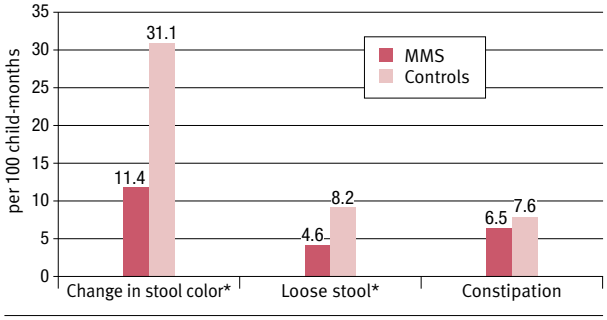
Among Bedouin infants, anemia rates decreased significantly from 58.8% to 40.6% ($P = 0.037$), with no statistically significant difference between study arms. However, there was a significantly different reduction in IDI prevalence between study arms over the 6 month intervention period: a decrease from 79.2% to 67.4% ($P = 0.010$) in the MMS group with no statistically significant change in the control group (from 84.5% to 86.4%, $P = 0.695$).

Among Jewish infants, the rates of anemia decreased significantly from 40.6% to 15.8% ($P = 0.017$) in both study arms with no statistically significant differences between intervention arms. The high IDI prevalence in this ethnic group decreased from 67% to 55.6% ($P = 0.046$) with no statistically significant differences between study arms.

Finally, we built multivariate logistic regression models using high IDI at 12 months as the outcome. We found that iron status at baseline was the strongest predictor for high IDI at age 12 months [Table 3] among both Bedouin and Jewish infants (odds ratio 2.81, $P = 0.003$, and OR 1.8, $P < 0.001$, respectively). In multivariate logistic regression analysis of the data in Bedouin infants, controlling for baseline iron status, MMS use was associated with a 67% reduced risk of high IDI at age 12 months as compared to standard supplementation (OR 0.33, $P = 0.001$). No effect of MMS compared to standard supplementation was found among Jewish infants [Table 3].

OR = odds ratio

Figure 1. Percent of months with reported side effects of supplementations by intervention groups (pooled Bedouin and Jewish children),*$P < 0.05$



Comparing the side effects reported by parents revealed fewer side effects in infants receiving MMS than in controls receiving oral supplementations. Significantly fewer parents of infants from the MMS arm as compared to controls reported loose stool and change in stool color [Figure 1].

DISCUSSION

To our knowledge, this is the first study to show the efficacy of a multiple micronutrient supplementation, "Sprinkles," as a home-food fortification in preventing anemia at age 1 year in an economically developed OECD country with universal, developed and available health services. We found unexpectedly high rates of anemia and high IDI among both Bedouin and Jewish infants at 6 months. The higher rates among Bedouin as compared to Jewish infants at baseline can be explained by lower maternal dietary iron intake [13], lower dietary iron intake in infancy, as shown in this paper [Table 2], and close spacing of Bedouin births [14] leading to depletion of maternal iron stores. In addition, iron flour fortification is not obligatory in Israel. This fact puts the population at higher risk for iron deficiency anemia [15].

The most important finding of the present study was that MMS supplementation in Bedouin children was associated with a 67% reduction in risk of iron deficiency at 12 months, when controlling for iron status at baseline, following 6 months of intervention with MMS as compared to standard supplementation with liquid iron and vitamin A and D. Since there are no previous studies on the efficacy of MMS in preventing anemia in developed countries, we compared our findings to studies using MMS in developing communities. The reduction in risk of iron deficiency at age 1 year among Bedouin infants in our study is consistent with findings from interventions in different underprivileged populations. In Ghana, among severely malnourished and anemic children who received daily MMS home fortification from age 6 to 12 months, the prevalence of moderate anemia (Hb < 10 g/dl) at 12 months was 31% in the control group compared to 10% in MMS groups ($P < 0.001$) [16]. In a similar study in Cambodia, MMS supplementation from 6 to 11 months of age was associated with a 27.1% decrease in moderate anemia [17]. In another study, Menon et al. [6] tested the effect of MMS in a malnourished pediatric population in rural Haiti and found that after the 2 month intervention the rates of anemia, adjusted for baseline prevalence, age and gender, dropped to 28% in the MMS group ($P < 0.001$) and increased to 45% in controls ($P = 0.07$).

The daily dose of iron in our MMS group was 12.5 mg of elemental iron as compared to 15 mg in the control group. In the study by Christofides and team [4], 12.5 mg of elemental iron as ferrous fumarate in MMS was as effective as 30 mg in decreasing rates of anemia in Ghanian infants aged 6–18 months with moderate anemia. They also showed that MMS supplementation was more effective than liquid iron drops (as we found in Bedouin infants).

Our study was carried out under ideal conditions, where both the MMS and liquid oral supplementations were provided free of charge at the clinics. Under usual clinical circumstances, the parents have to go to the pharmacy and pay a small fee for the supplementation. Since MMS is associated with better acceptability [8] and lower rates of reported side effects, as reported in this study, it is possible that if parents were given the choice of obtaining MMS or oral liquid drops (for the same cost), compliance rates would increase.

Another advantage of MMS is that it contains the micronutrients folic acid, vitamin C (for enhancing iron absorption), and zinc, in addition to vitamins A and D. This is potentially very important for populations of low socioeconomic status that have a less micronutrient-rich diet and multiple micronutrient deficiencies [18,19].

In light of our findings, we recommend that home-food fortification of infant food with MMS in the form of a powdered single-use daily serving be used as an effective and safe method to prevent anemia. We believe it is the preferred method of supplementation for infants from low socioeconomic backgrounds.

OECD = Organisation for Economic Co-operation and Development

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