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Anemia as a risk factor for infectious diseases in infants and toddlers: Results from a prospective study

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Abstract. Anemia due to iron deficiency is the most prevalent form of micronutrient malnutrition in the world, however, the causal relationship between anemia and infection remains unclear. We examined prospectively, the association between anemia and infection among Bedouin infants. We recruited 293 families and newborns from the Bedouin population, which is ongoing major lifestyle changes, during the periods of 1989–1992 and 1994–1997 and followed them to age 18 months. The number of diarrhea and respiratory disease episodes as well as total days of diarrhea were ascertained weekly. Hemoglobin levels were obtained at age 6 months. Additional data on feeding practices, environmental, household and demographic characteristics were obtained throughout the 18 months. Diarrhea before 6 months of age was found to be a risk factor for diarrhea after that age. After controlling for early morbidity $<$ 6 months, anemia (Hb $<$ 11 g/dl) at 6 months was an independent risk factor for diarrhea and respiratory illness from 7 to 18 months of age. This associations remained significant even after controlling, in addition, for environmental and socio-economic factors. In the multivariable models, anemia at age 6 months increased the risk for diarrhea after that age by 2.9-fold (95% confidence interval 1.6–5.3; $p = 0.001$) and that of respiratory disease by 2-fold (1.1–3.7; $p = 0.03$). Our findings suggest that anemia may increase the rates of infections in toddlers. The possibility that reducing anemia in infants may be a preventive measure to lower disease burden from infectious disease in this and other vulnerable populations should be tested in further studies.

Key words: Children, Cohort study, Diarrhea, Negev Bedouins, Respiratory diseases

Introduction

Iron deficiency anemia (IDA) is the commonest form of malnutrition worldwide, affecting 43% of the world's children. It is particularly common in Asia and Africa [1] but is prevalent in low socio-economic populations in developed countries as well [1–3]. In infants it has wide-ranging adverse consequences including impaired physical growth and compromised cognitive development. Anemia is also associated with a short attention span and impaired learning capacity [4].

The prevalence and causes of anemia among Israeli children have been studied during the last three decades [5–8]. In the 1970s, rates of anemia were high among Jewish children, and were shown to be associated with low socio-economic status [5]. In the 1980s, anemia rates among Arab infants ranged from 19 to 71% and among Jewish children the rate was about 60% [6, 7]. As a result, in the mid 1980s the Israeli Ministry of Health recommended giving iron supplements to all infants age 5–12 months. Studies published in the early 1990s showed that the rates of anemia had decreased in various intervention areas [8]. Recently the Israeli Ministry of Health concluded that anemia in Israeli infants is due largely to iron deficiency [9]. This is due to the facts that alternative causes for anemia are rare in Israeli children and anemia in general improved following supplementation. A recent study examined nutritional status in 534 healthy Bedouin children aged 1–2 years of age attending Ministry of Health Well Infant and Mother Clinics, for routine vaccination [10]. While 27% of the children were anemic (hemoglobin levels 11 g/dl), only 11.5% had zinc deficiency (<60 μg/dl). When comparing the median value for American 2 year olds from the NHANES II study [11] we find that it is <85 μg/dl as compared with our data of 89 μg/dl. Furthermore the mean ($\pm$ SE) values for serum zinc levels were 82.5 ($\pm$ 0.3) and 94.1 ($\pm$ 1.3) for US children and the Bedouin group, respectively. These data suggest that while zinc may contribute to anemia in the Bedouin population iron deficiency has a more decisive role than does zinc. We therefore consider hemoglobin levels under 11 g/dl in the cohort infants as anemia due to iron deficiency.

In the Negev area, Bedouin children have higher rates of anemia than Jewish children [7] as well as higher rates of hospitalizations from infectious diseases, especially in the first 2 years of life [12]. In general, respiratory illness and diarrhea are the main causes of morbidity and mortality in infants and children in less developed countries [13, 14] and pose a heavy burden on health care services in developed and less developed countries alike [15]. The causal relationship between iron status and susceptibility remains unclear [16, 17]. The directionality of this association is difficult to establish as infection lowers hemoglobin levels and children may become anemic as a result of repeated infections. This relationship is further confounded by environmental and socio-economic variables which themselves are risk factors for both anemia and infection.

The Bedouin population in southern Israel is in a process of transition from nomadic to western life style, a process affecting nutritional practices and health status similar to that in other transitional populations. The Bedouin population has higher crude birth rates and higher infant mortality rates, as well as other indicators of socio-economic disadvantage relative to the general Israeli population [18] and therefore can serve as a model for other disadvantaged populations. A prospective study performed among Bedouin infants and young children who were followed from birth during two periods of time, allows us to examine the causal association between anemia and infection in infants and toddlers. The status of anemia was determined at 6 months of age and its role in subsequent infection examined. The study design also allowed us to control for history of infection prior to 6 months of age, as well as for other environmental and socio-economic factors associated with anemia and infection. Thus this analysis attempted to disentangle the anemia infection causal web.

Subjects and methods

This study was conducted in a town located 35 km from Beer-Sheva, the capital of the Negev in southern Israel. The town was the first urban settlement of Bedouin tribes and today has well-developed community preventive and curative health-care facilities. This study includes infants from the town who were born at the Soroka University Medical Center (SUMC) in Beer-Sheva. SUMC is the only tertiary care institution in the area and provides both delivery and post-delivery care. Close to 100% of women in the Negev, both Jewish and Bedouin, deliver at this hospital. The study cohort includes healthy infants, birth weights ≥2500 g who were enrolled on the days following delivery after informed consent was obtained from the mother. For administrative reasons infants were recruited from November 1989 to December 1992 and then from December 1994 to March 1997.

Throughout the study, monthly home visits were made, at which time questionnaires were completed by trained Arabic speaking interviewers to obtain information about the feeding habits of the infant and his/her health in the preceding month. At the age of 3 months an environmental assessment was performed. This included observations regarding the environmental condition of the home and the yard, as well as the presence of animals. In addition, the physical condition of the home and the availability of water, toilet facilities and electricity were noted. Other observations included the hygienic condition of the infant and kitchen. A prosperity score was developed by summing nine items, each contributing 1 point, so that the higher the score the more prosperous the family was considered to be. The items that constitute the prosperity score are: type of dwelling (brick house/tent or hut), type of floor (tiles/cement or beaten earth), water supply (in-door/out-door), toilet facilities (in-door/out-door), electricity (yes/no), refrigerator (yes/no), washing machine (yes/no), food storage (cupboard/open shelves) and kitchen utensil storage (cupboard/open shelves).

The infectious disease (diarrhea and respiratory illness) surveillance methods have been described in detail elsewhere [19]. In short, episodes of illness were identified via a surveillance network that was established at all health care locations in the study area and was supplemented by maternal reports at monthly home visits. In addition, diarrhea episodes were ascertained during weekly interviews. For families recruited from 1994, morbidity surveillance was via weekly home interviews. When a diarrhea episode was noted, morbidity questionnaires were completed, which included information about episode duration and symptoms, medication and health care utilization. The definition of a diarrhea episode was the passing of ≥3 soft stools in a 24 h period, except for infants aged ≤1 month, for whom the definition was ≥4 soft stools in 24 h. A new episode was identified as preceded by at least 3 days without diarrhea. High diarrhea morbidity was defined as 20 or more illness days with diarrhea between the ages of 7–18 months, which was the upper quartile for the distribution of total days of diarrhea illness.

Maternal reports of signs and symptoms regarding respiratory infections such as cold, tonsillitis, asthma, bronchitis and pneumonia were used to define respiratory infection episodes. Acute otitis media was evaluated separately. A high number of respiratory episodes or otitis media episodes were defined as 5 or more episodes between the ages of 7–18 months. These cut-off points represent the upper quartile for the distribution of the number of respiratory episodes or otitis media episodes.

When infants reached 5 months of age, the mothers were invited to obtain a blood test to determine the infant's hemoglobin level. A primary care physician in the mother and child health care clinics took the venous blood samples and the tests were performed in the routine hematology laboratory of SUMC. Anemia was defined according to the World Health Organization standard as hemoglobin level of < 11.0 g/dl [20].

Statistical methods

Comparisons of categorical variables were performed using the χ^2 test or Fisher Exact test as appropriate. ANOVA or the Student's *t*-test were used for continuous variables. Odds ratios (OR) with 95% confidence intervals (95% CI) were computed to assess relative risk. Multiple logistic regression analysis was used to assess odds ratios for independent risk factors while controlling for potential confounders.

Results

A total of 521 were enrolled at birth, of these families of 23 infants (4.4%) who had signed informed consent forms could not be located or their homes could not be reached on a regular basis. Twenty six (5.2%) families dropped out at various stages due to unwillingness to continue or because of frequent and prolonged absences from the home address. A total of 472 (90.6%) of the infants entering the study completed at least 18 months of follow-up. Of those, 293 (62.1%) infants had a blood test for hemoglobin level between the ages of 5 and 7 months and are included in this analysis.

No statistically significant differences for any of the socio-demographic characteristics or morbidity related variables were found when we compared infants from whom a blood test at age 6 months (± 1 month) was obtained to those for whom a test was not available. The parameters included birth weight, gender, gestational age, number of other children in the family, maternal age and education, prosperity score, duration of breastfeeding, number of diarrhea episodes and number of respiratory episodes experienced. Thus the children with hemoglobin measures appear to represent the study cohort.

Most of the families of these 293 children (92%) lived in brick houses, but 22 (8%) resided in a hut or a traditional Bedouin tent. In 63 (22%) of the homes, the floor was beaten earth, 45 (15%) had only outdoor toilets and 17 (6%) had no electricity. All homes had access to a safe water supply via Israel's main water supply, but in 22 (8%) of the homes the taps were located outdoors. The mean age of weaning was 9.7 months (SD 6.0; median 9.0), however mothers introduced milk supplements at an average age of 2.0 months (SD 2.8; median age 1.0 months).

As the Bedouin population is undergoing rapid changes in lifestyle, we decided to compare the socio-demographic characteristics of the families enrolled during 1989–1992 (period 1) with those enrolled during 1994–1997 (period 2). Data from the two periods were similar with regard to maternal age, number of children in the family, birth weight and gestational age, gender composition and duration of breast-feeding of the index infant. We found statistically significant differences for maternal education and the prosperity score, both being higher during 1994–1997 (Table 1).

Morbidity (diarrhea and respiratory) was examined by socio-demographic and environmental characteristics. The morbidity indicators compared in the study were number of diarrhea episodes and total number of days of diarrhea, as well as number of respiratory episodes. There was no association between morbidity and variables such as gender, weight-for-age at 6 months, maternal age at childbirth and the prosperity score.

In order to examine the association between anemia and socio-demographic and environmental characteristics, and the morbidity experience of the infants before 6 months of age, we compared these parameters between anemic and non-anemic children at 6 months of age (Table 2). Mothers of anemic

Table 1. Comparison of socio-demographic characteristics of Bedouin infants between families enrolled during 1989–1992 and 1994–1997. Values are mean ± SD unless otherwise stated

Variable	Enrolled during 1989–1992 N = 153	Enrolled during 1994–1997 N = 140	*p*-Value
% Males	51.0%	53.6%	0.74
Birth weight (gr.)	3283 ± 421	3275 ± 411	0.87
Gestational age (weeks)	39.6 ± 1.4	39.4 ± 1.7	0.13
Parity	3.4 ± 3.3	3.3 ± 2.3	0.74
Maternal age (years)	27.3 ± 7.0	27.5 ± 5.7	0.75
Maternal years of education	4.2 ± 4.4	6.4 ± 4.0	< 0.01
Prosperity score (range: 1–9)[a]	6.3 ± 2.4	7.3 ± 2.2	< 0.01
Duration of breastfeeding (months)	9. 8 ± 5.6	9.5 ± 5.6	0.72

[a]Prosperity score: sum of nine items, where the higher score represents a family with more modern living conditions (type of house, type of floor, water supply, toilet facilities, electricity, refrigerator, washing machine, food storage and kitchen utensil storage).

Table 2. Comparison of sociodemographic characteristics of children with anemia (Hb < 11.0 g/dl) and those without anemia (Hb ≥ 11.0 g/dl) at 6 months of age. Values are mean ± SD unless otherwise stated

Variable	Non anemic N = 165	Anemic N = 128	*p*-Value
% Males	47.9%	57.8%	0.09
Birth weight (gr.)	3262 ± 426	3300 ± 403	0.43
Gestational age (weeks)	39.6 ± 1.6	39.4 ± 1.4	0.38
Parity	3.3 ± 2.6	3.5 ± 3.1	0.58
Maternal age (years)	27.5 ± 5.8	27.3 ± 7.0	0.86
Maternal years of education	5.9 ± 4.4	4.4 ± 4.2	0.01
[a]Prosperity score (range: 1–9)	7.0 ± 2.3	6.5 ± 2.3	0.08
Duration of breastfeeding (months)	9.4 ± 6.1	10.1 ± 5.9	0.31
Weight-for-age *Z* scores at 6 months	−0.09 ± 0.89	−0.11 ± 0.90	0.81
No. of diarrhea episodes 0–6 months	0.6 ± 0.9	0.7 ± 1.1	0.28
[b]No. of reported respiratory episodes 0–6 months	3.0 ± 2.5	3.9 ± 2.9	0.01
No. of reported otitis media episodes 0–6 months	0.91 ± 1.14	0.88 ± 1.19	0.81

[a]Prosperity score: sum of nine items, where the higher score represents a family with more modern living conditions (type of house, type of floor, water supply, toilet facilities, electricity, refrigerator, washing machine, food storage and kitchen utensil storage).

[b]Respiratory episodes: cold, tonsillitis, asthma, bronchitis and pneumonia.

infants had lower mean years of education as compared with non-anemic infants (4.4 vs. 5.9 years; $p = 0.01$). The families of anemic infants also had a lower mean prosperity score than the non-anemic infants, but this was not statistically significant ($p = 0.08$). No difference in diarrhea morbidity up to age 6 months was found between anemic and non-anemic children, but there were more reported respiratory illnesses among the anemic children.

To determine the causal association between anemia and morbidity from infectious disease, we studied the effect of anemia at age 6 months on morbidity for ages 7–18 months (Table 3). Infants anemic at 6 months had more episodes of diarrhea and more days of diarrheal illness per child, as well as more respiratory, and otitis media episodes between 7 and 18 months of age.

A multivariable logistic analysis was performed to determine the independent effect of anemia on morbidity (Table 4). The association between anemia at 6 months and subsequent illness was examined controlling for maternal age and education, parity, the child's gender, breast-feeding duration, weight-for-age *Z* score at 6 months, having experienced at least one diarrhea episode before 6 months of age, having experienced at least one respiratory episode before 6 months of age and the prosperity score. After controlling for environmental factors, the independent risk factors for at least 1 diarrheal episode between ages 7 and 18 months were: anemia at 6 months and at least one diarrhea episode before age 6 months. In addition to these two variables, maternal education of ≤ 8 years was an independent risk factor for ≥20 days of diarrhea between ages 7 and 18 months (OR:3.32 (95% CI: 1.37–8.02), $p = 0.008$). Anemia was also an independent risk factor for ≥5 respiratory and otitis media episodes between ages 7 and 18 months. Duration of breastfeeding was inversely associated with risk of respiratory disease while maternal education of ≤ 8 years was a risk factors for otitis media. Having experienced at least one respiratory episode before 6 months of age, was a risk factor for respiratory episode after that age as well as for otitis media.

Additional multivariable logistic models were run to determine the effect on infections prior to

Table 3. Comparison of infectious disease occurrence during ages 7–18 months in children with anemia (Hb < 11.0 g/dl) and those without anemia (Hb ≥ 11.0 g/dl) at 6 months of age

Morbidity ages 7–18 months	Non anemic N = 165 mean ± SD	Anemic N = 128 mean ± SD	*p*-Value
No. of diarrhea episodes	1.3 ± 1.5	2.2 ± 2.0	<0.01
Total No. diarrhea days per child	9.7 ± 14.5	17.6 ± 17.7	<0.01
[a]No. of reported respiratory episodes	2.4 ± 2.6	3.6 ± 3.3	<0.01
No. of reported otitis media	2.4 ± 2.2	3.4 ± 2.9	<0.01

[a]Respiratory episodes: cold, tonsillitis, asthma, bronchitis and pneumonia.

Table 4. Multiple logistic regression models for association of anemia (Hb < 11 compared to ≥ 11 g/dl) at age 6 months with subsequent morbidity (ages 7–18 months). Odds ratios (OR) and 95% confidence intervals (95% CI) are presented. All models are adjusted for maternal and environmental variables[a]

Model No.	Morbidity outcome variable (age 7–18 months)	Risk factors	OR (95% CI)	*p*
1	Any diarrhea episode	Anemia at 6 months	2.87 (1.57–5.26)	0.001
		≥ 1 diarrhea episode up to 6 months	2.79 (1.52–5.12)	0.001
		≥ 1 respiratory illness up to 6 months	1.01 (0.45–2.28)	0.97
2	≥ 20 days of diarrhea	Anemia at 6 months	3.38 (1.81–6.31)	< 0.001
		Maternal education[b]	3.32 (1.37–8.02)	0.008
		≥ 1 diarrhea episode up to 6 months	2.81 (1.51–5.22)	0.001
		≥ respiratory illness up to 6 months	1.36 (0.54–3.41)	0.51
3	≥ 5 episodes of respiratory illness	Anemia at 6 months	1.99 (1.07–3.71)	0.03
		Breast feeding duration (months)	0.93 (0.88–0.98)	0.01
		≥ 1 diarrhea episode up to 6 months	1.41 (0.75–2.63)	0.28
		≥ 1 respiratory illness up to 6 months	3.94 (1.14–13.64)	0.03
4	≥ 5 episodes of otitis media	Anemia at 6 months	2.23 (1.19–4.19)	0.01
		Maternal education[b]	2.70 (1.08–6.72)	0.03
		≥ 1 diarrhea episode up to 6 months	2.00 (1.07–3.76)	0.03
		≥ 1 respiratory illness up to 6 months	1.47 (0.56–3.87)	0.44

[a]Gender, child's weight-for-age *Z* score at 6 months, maternal age and education, parity and prosperity score.
[b]Maternal years of education (≤ 8 vs. ≥ 9 years).

6 months of age when anemia is excluded from the models. The models included the same variables as the full models presented in Table 4 excluding anemia at 6 months. Very little change was seen in any of the model parameters when anemia was excluded. The OR for illness variables up to 6 months of age did not change by > 6.4% in any of the new analyses. The OR's (95% CI, and percent change in the OR excluding anemia) for diarrheal illness in the models for any diarrhea episode (model 1), for ≥20 days of diarrhea (model 2), and for ≥5 episodes of otitis media (model 4) were 2.75 (1.51–4.99; −1.5% change), $p = 0.001$, 2.63 (1.46–4.76; −6.4% change), $p = 0.001$, and 1.98 (1.07–3.67; −1% change), $p = 0.03$, respectively. The OR estimate for respiratory illness in the first 6 months of life as a risk factor for subsequent respiratory morbidity also remained unchanged, with OR (95% CI and percent change in the OR excluding anemia) of 3.85 (1.12–13.28; −2.3% change) $p = 0.003$.

Discussion

In this study, we examined the data of Bedouin infants in southern Israel who were followed from birth to age 18 months, to determine the causal relationship between anemia and infectious disease morbidity while controlling for environmental and socio-economic factors. We assessed anemia at 6 months of age as a risk factor for infections that occurred between 7 and 18 months of age. The study design also allowed us to control for history of infections from birth up to age 6 months, prior to the detection of anemia, as well as for environmental and socio-economic factors.

We found among Bedouin infants that anemia is an independent risk factor for diarrhea and respiratory illness. Thus anemic infants had a 3-fold risk for any diarrhea episode and for 20 or more days of diarrhea following the development of anemia. In addition, we found that anemia resulted in a 2-fold risk for more respiratory episodes. We suggest therefore, that anemia is a significant and independent risk factor for diarrhea as well as for respiratory illness, even after controlling for environmental and socio-economic factors.

Infections are a well-recognized cause of mild to moderate anemia [21]. Several studies have demonstrated that even mild infections can induce a significant decrease in iron levels [22, 23]. The reduction in hemoglobin level during and after acute or chronic inflammatory diseases is due to factors such as blocking the iron release or reduction in intestinal absorption of iron and inhibition or inappropriate erythropoietin production [24].

Acute infections are frequent in childhood, especially in low socio-economic populations, and may be one of the causes of high anemia rates. Relative to the general Israeli population, the Bedouins have higher crude birth rates and higher infant mortality rates, as well as other indicators of socio-economic disadvantage [18]. Arab Bedouin children have been shown to suffer from high rates of stunting [25, 26] as well as high rates of illness from infectious diseases [12, 19, 27, 28]. In the years in which our study was performed, the rate of hospitalized infectious diseases in Bedouin infants was 1722 per 10,000 as compared to 720 in Jews, and Bedouin infants had a 2.7 fold risk for being hospitalized with infectious diseases as compared to Jewish infants [12].

As Bedouin children do not suffer from high rates of zinc deficiency (11.5%) while having high rates of anemia (27%), we feel that the issue of iron deficiency is the one that should be addressed in this study. The interaction between iron status, iron supplementation and susceptibility to infection remains unresolved [16, 17]. Because of issues of confounding, few observational clinical studies in iron-deficient humans convincingly relate such deficiency to substantial infections and morbidity [17]. This issue if further complicated by co-deficiencies of other micronutrients such as zinc where iron supplementation may even increase morbidity [29]. Our study, like several others in non-malarias areas, has shown an association between iron deficiency anemia or iron deficiency and infections [30–34]. Iron deficiency has been shown to impair immune function and to increase the risk of infection [30]. Moreover, anemic children are reported to have a higher incidence of gastroenteritis, respiratory infection, otitis media and meningitis, but these children may have been anemic because of their repeated infections [2, 17, 31–33]. Other studies have noted anemia in children admitted to hospital for various infections, but these data could not establish causality [17, 34].

On the other hand, it has been proposed that there is an inverse association between iron deficiency anemia and diseases [16, 17, 35, 36]. Since iron deprivation in bacterial cultures is associated with in vitro inhibition of bacterial growth, it has been suggested that iron deficiency may offer 'nutritional immunity' and be an important defense mechanism against infection [35, 36]. In practice, however, this thesis appears to have been overstated for extra-cellular microbial pathogens, although iron treatment has been associated with acute exacerbations of infection, in particular, malaria. In his comprehensive review Oppenheimer mentioned that oral iron has been associated with increased rates of clinical malaria (5 of 9 studies) and increased morbidity from other infectious disease (4 of 8 studies) [17].

The complex cause and effect relationship between iron deficiency and infection is further confounded by environmental and socio-economic variables which themselves may predispose to both anemia and infection [2]. In our study we examined child and family characteristics, as well as environmental and socio-economic factors to determine the factors associated with anemia in this population. Anemia in study infants was associated with low maternal education and a borderline association with low prosperity score was also found. These results are consistent with evidence from other studies, which show an association between maternal education or socio-economic status and childhood anemia [5, 37].

In order to examine the cause and effect relationship between anemia and infectious diseases, data from a prospective follow-up study are needed. Our study design, in which infants' morbidity was monitored before and after hemoglobin level ascertainment, provided an opportunity to examine not only the association, but also the cause and effect relationship between iron deficiency anemia and infections. The data demonstrated that anemia at 6 months was significantly associated with morbidity at ages 7–18 months after controlling for previous infections as well as environmental and socio-economic variables. Furthermore, the results show that illness prior to 6 months and anemia are independent predictors for subsequent morbidity. As the risk estimates for morbidity at ages 0–6 months do not change when anemia is excluded from the multivariable models we conclude that the two risk factors are highly likely to be independent. Additional prospective studies in different populations are required however, to confirm these findings.

A limitation of this study is that iron deficiency anemia was not measured directly. Instead, hemoglobin level was used to assess the presence of iron deficiency anemia. The use of this measure as an indicator of iron deficiency status has sparked debate, especially in areas where the prevalence of iron deficiency is low [38]. However in Israel, the other possible causes for anemia are not prevalent, and the Ministry of Health defines anemia in infants as iron deficiency anemia [9].

Infectious diseases pose a heavy burden on health services in developing and developed countries [15, 39]. Our results add weight to the accumulating evidence of the importance and potential impact of reducing iron deficiency anemia in infants as a measure in lowering the infectious disease burden in populations. The possibility that reducing anemia in infants may be a preventive measure to lower disease burden from infectious disease in this and other vulnerable populations should be tested in further studies.

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