Effects of maternal micronutrient supplementation on fetal loss and infant mortality: a cluster-randomized trial in Nepal"1–3

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ABSTRACT
Background: We previously reported that maternal micronutrient supplementation in rural Nepal decreased low birth weight by ~15%.
Objective: We examined the effect of daily maternal micronutrient supplementation on fetal loss and infant mortality.
Design: The study was a double-blind, cluster-randomized, controlled trial among 4926 pregnant women and their 4130 infants in rural Nepal. In addition to vitamin A (1000 μg retinol equivalents), the intervention groups received either folic acid (FA; 400 μg), FA + iron (60 mg), FA + iron + zinc (30 mg), or multiple micronutrients (MNs; the foregoing plus 10 μg vitamin D, 10 mg vitamin E, 1.6 mg thiamine, 1.8 mg riboflavin, 2.2 mg vitamin B-6, 2.6 μg vitamin B-12, 100 mg vitamin C, 64 μg vitamin K, 20 mg niacin, 2 mg Cu, and 100 mg Mg). The control group received vitamin A only.
Results: None of the supplements reduced fetal loss. Compared with control infants, infants whose mothers received FA alone or with iron or iron + zinc had a consistent pattern of 15–20% lower 3-mo mortality; this pattern was not observed with MNs. The effect on mortality was restricted to preterm infants, among whom the relative risks (RRs) were 0.36 (95% CI: 0.18, 0.75) for FA, 0.53 (0.30, 0.92) for FA + iron, 0.77 (0.45, 1.32) for FA + iron + zinc, and 0.70 (0.41, 1.17) for MNs. Among term infants, the RR for mortality was close to 1 for all supplements except MNs (RR: 1.74; 95% CI: 1.00, 3.04).
Conclusions: Maternal micronutrient supplementation failed to reduce overall fetal loss or early infant mortality. Among preterm infants, FA alone or with iron reduced mortality in the first 3 mo of life. MNs may increase mortality risk among term infants, but this effect needs further evaluation.

KEY WORDS Micronutrients, pregnancy, supplementation, fetal loss, infant mortality

INTRODUCTION
Infant mortality reduction remains a major public health goal throughout the developing world. Postneonatal mortality has declined globally, in contrast with neonatal mortality, which constitutes one-half of all infant deaths in many developing countries (1, 2). In general, populations with high infant mortality also have a high prevalence of low birth weight (< 2.5 kg) (3), a condition that predisposes newborns to increased neonatal mortality (4–6) and morbidity (7–10).

There is little causal evidence on the effect of maternal micronutrient supplementation on pregnancy outcome and infant health and survival in the developing world. Although prenatal multivitamin and mineral supplements are commonly consumed in developed countries, this practice is less common in developing countries, in which existing antenatal iron-folate programs achieve low coverage and have been ineffective in reducing maternal anemia (11). In fact, the issue of a lack of efficacy and safety of routine iron supplementation has been raised (12). Both low and high hemoglobin concentrations during pregnancy are associated with adverse outcomes, and yet it is not known whether iron supplementation decreases or increases the risk of adverse outcomes (13, 14). Of the 23 iron-intervention studies reviewed by Rasmussen (14), none were free from possible bias, and many suffered from problems with design and interpretation. Furthermore, in several studies, the lowest rates of low birth weight and preterm birth occurred at hemoglobin concentrations that were below the current cutoffs for anemia during pregnancy (14). Thus, the efficacy of iron supplementation during pregnancy needs to be urgently assessed with the use of endpoints such as low birth weight, preterm delivery, and infant mortality, and not just anemia. Folic acid is added to antenatal iron but may have an independent role in enhancing birth outcomes. An overview of 5 controlled trials suggested a 41% reduction in the prevalence of intrauterine growth retardation with folic acid supplementation,

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although these trials were small and their study designs have been called into question (15). Trials in Bangladesh (16) and Peru (17) failed to confirm the improvement in birth weight found in previous studies of antenatal zinc supplementation (18, 19). A move toward multiple micronutrient supplementation is currently taking place. UNICEF has recently developed such a supplement, which is catered to pregnant women in developing countries and is being proposed for wide-scale use and distribution. Yet, the benefits of such a supplement are not well established.

In a randomized trial of women in a poor, malnourished, rural population in Nepal, we previously reported the effects on birth weight of daily consumption of 4 different combinations of antenatal micronutrient supplements (20). The treatment arms were as follows: control, folic acid, folic acid + iron, folic acid + iron + zinc, and folic acid + iron + zinc + 11 other vitamins and minerals. Each supplement type also contained vitamin A, which we previously found to reduce the risk of maternal mortality (21) but to have no effect on neonatal weight (KP West Jr, unpublished observations, 2003) or infant mortality (22). Compared with the control group, only the folic acid + iron group and the multiple micronutrient supplement group had lower incidences of low birth weight (16% [relative risk (RR): 0.84; 95% CI: 0.72, 0.99]) and 14% (RR: 0.86; 95% CI: 0.74, 0.99) lower, respectively; none of the treatments had any effect on preterm delivery (20).

In this article, we report from the same study on the effect of these alternative micronutrient supplement regimens on fetal loss and perinatal, neonatal, and 3-mo mortality. The objective was to determine whether a micronutrient intervention that decreased low birth weight by \( \approx 15\% \) also improved survival among infants. Although the treatments failed to prevent preterm birth, we examined treatment effects on mortality stratified by preterm (< 37 wk of gestation) and term births to examine possible interactions.

SUBJECTS AND METHODS
Study design and population

The study was a cluster-randomized, double-blind trial that featured an active control group and was conducted in the rural plains district of Sarlahi, Nepal, to examine the effect of prenatal and postnatal maternal supplementation on birth weight, fetal loss, and early infant mortality. This is the same area of Nepal in which we previously recorded evidence of vitamin A, iron, and zinc deficiency among pregnant women. The study area, comprising 30 village development communities with a total population of \( \approx 200,000 \), was divided into 426 smaller communities called “sectors,” which served as the units of randomization. Randomization was done in blocks of 5 within each village development community by the senior study investigators, who drew numbered chips from a hat. At the outset, women who were sterilized, widowed, menopausal, or breastfeeding an infant < 9 mo of age were considered to have a low risk of becoming pregnant and were excluded from the study. The remaining women were visited once every 5 wk by 426 locally hired female workers (called “sector distributors”), who ascertained pregnancies by offering a human chorionic gonadotropin–based urine test to those who reported having not menstruated in the previous 30 d. A positive urine test and informed consent resulted in a woman being enrolled into the study to receive supplements. Enrollment of pregnant women took place from January 1999 through February 2000. A baseline interview was conducted to obtain the date of the last menstrual period and diet, morbidity, and work histories in the preceding week and to collect data on socioeconomic status and reproductive history. Gestational age was calculated by using the date of the last menstrual period, which was verified against the prospectively collected data on menstrual history as well as the date of the positive pregnancy test. Anthropometric assessment, including measurements of weight, height, and midupper arm circumference, was also performed at baseline. Assessment at birth of all liveborn infants included anthropometric measurements (within 72 h) and a history of labor and delivery and symptoms in the newborn immediately after birth.

Ethical approval for the study was provided by the National Health Research Council of the Ministry of Health, Kathmandu, Nepal, and the Committee for Human Research at the Johns Hopkins Bloomberg School of Public Health, Baltimore. A Data Safety and Monitoring Committee meeting took place midway through the study, and continuation of the study was approved.

Intervention

The sectors were randomly assigned to 1 of 5 treatment arms. All the women in the study received vitamin A because it reduced pregnancy-related mortality by 40% (21) but did not affect fetal loss or infant mortality (22). The 5 treatment arms were as follows: control, vitamin A (1000 \( \mu \)g retinol equivalents); FA, vitamin A + folic acid (400 \( \mu \)g); FAFe, vitamin A + folic acid + iron (60 mg); FAFeZn, vitamin A + folic acid + iron + zinc (30 mg); MN, vitamin A + folic acid + iron + zinc + other micronutrients (10 \( \mu \)g vitamin D, 10 mg vitamin E, 1.6 mg thiamine, 1.8 mg riboflavin, 20 mg niacin, 2.2 mg vitamin B-6, 2.6 \( \mu \)g vitamin B-12, 100 mg vitamin C, 65 \( \mu \)g vitamin K, 2.0 mg Cu, 100 mg Mg).

The supplements, which were of identical shape, size, and color, arrived in Nepal in opaque, sealed, and labeled bottles coded 1–5. The code allocation was kept locked at the Johns Hopkins University, Baltimore. The investigators, field staff, and participants were blinded to the codes throughout the study.

At the outset of the study, each pregnant woman received a small bottle containing 15 supplement caplets, with instructions from the staff to take 1 supplement/d. The women were subsequently visited twice each week by the sector distributors, who replenished the caplets, monitored their consumption, and collected data on pregnancies and their outcomes. The supplements were to be taken daily from the time of pregnancy detection through 3 mo postpartum in the case of a live birth and through \( \approx 5 \) wk after a miscarriage or stillbirth.

A sample size estimate of 1000 pregnant women per group was based on detecting an increase in birth weight of \( \approx 75 \) g with 80% power after a 10% fetal loss, a 15% loss to follow-up, and a 20% design effect estimated from our previous study (21, 22; KP West Jr unpublished observations, 2003) were accounted for. With this sample size and an assumption that the fetal loss rate and the infant mortality rate among the control subjects were 10% and 75 deaths/1000 live births, respectively (22), a reduction in fetal loss of \( \geq 34\% \) and a reduction in infant mortality of \( \geq 45\% \) would be detected with a type 1 error of 5% and 80% power.

During the first 3 mo of life, the vital status of the infants was assessed every week. For all the liveborn infants and their
mothers, a 6-mo postpartum home visit was conducted to assess vital status. The study was completed in April 2001 when the last infant born in the study had been followed through 6 mo of life. The vital status of all the infants was also assessed at that time. At the end of the study, \( \approx 70\% \) of the infants across all treatment groups had been followed for \( \geq 364 \) d. Miscarriage was defined as a pregnancy that ended in a fetal loss before 28 wk of gestation. We defined perinatal mortality to include stillbirths (gestational age of \( \geq 28 \) wk) and deaths through the first 7 d of life. This definition also included stillbirths (\( n = 8 \)) that accompanied a liveborn infant among twin births. Neonatal mortality was defined as deaths among live births through 28 d of life.

Data from verbal autopsy interviews and infant morbidity assessments conducted on the day of birth were used to assign the cause of death. A verbal autopsy was usually performed within a week after an infant death was reported. Thirty well-trained and experienced workers, who had previously conducted interviews by using the same verbal autopsy instrument for \( \approx 800 \) infant deaths in our previous study, were responsible for administering the verbal autopsy interviews in the present study. Causes of death were elicited by using a 2-step procedure. First, 2 physicians conducted an independent review of verbal autopsy interviews and assigned a cause of death. Differences in the assigned causes were reconciled by discussion between the reviewers. We were unable to assign causes for 84 (of 174) neonatal deaths by using this process. The number of cases for which we did not have a cause of death did not differ by treatment group. For 59 of these 84 deaths, illness symptoms at birth were further used to assign a cause of death on the basis of published algorithms (23). These causes of death were prematurity or severe malnutrition and birth asphyxia. Death was attributed to prematurity or severe malnutrition if the gestational age was \( < 32 \) wk or the birth weight was \( < 1.5 \) kg. Death was attributed to birth asphyxia if 1) the infant died within 7 d and did not cry or cried weakly at birth and was not able to breathe after birth, or the infant had convulsions or was unable to suckle; 2) the infant died within 7 d and either had convulsions or had a breather presentation, or the woman had prolonged labor (\( > 24 \) h) or obstructed labor; or 3) the infant died within the first day of life and had a blue body or pale extremities. Cause-specific neonatal mortality rates were calculated by treatment group.

Health care

All the pregnant women in the study received counseling on antenatal care and nutrition at the time of enrollment. The women were encouraged to visit health posts and to take iron supplements during pregnancy. The policy in Nepal is for all pregnant women visiting health posts to receive iron supplements, although coverage and adherence are poor (24). Because we previously found that hookworm was one of the strongest etiologic factors for anemia (25), we provided deworming medicine to all the pregnant women in the second and third trimesters of pregnancy. The women received a tetanus toxoid vaccination twice during pregnancy, a safe birthing kit for home-based delivery from the United Nations Children’s Fund, and a flannel blanket for their newborns. In a 20% subsample, from whom venous blood was drawn at baseline and in the third trimester to measure biochemical indicators of nutritional status, all severely anemic women (hemoglobin \(< 70 \) g/L) at both times received 90 d of treatment with 120 mg Fe and 400 \( \mu \)g folic acid.

Statistical analysis

Characteristics of the pregnant women and their compliance with supplementation, which was defined as the proportion of all eligible doses that were consumed, were compared across treatment groups. All analyses were done on an intention-to-treat basis. Multiple births in the study (\( n = 42 \)) were included in the analysis because their inclusion did not alter the study results.

Kaplan-Meier survival analysis (26) was used to estimate and compare differences in the survival probabilities of liveborn infants from birth through 364 d of life by treatment group. Infants were censored from the survival analysis at the time when their vital status was last known. Deaths and follow-up time for survivors beyond 364 d were excluded from the analysis. RRs and 95% CIs for fetal loss and perinatal, neonatal, and 0–3-mo mortality rates were calculated by using a generalized estimating equations (27) binomial regression model with log link and exchangeable correlation to adjust for the design effect and with the mortality rate among the control (vitamin A) subjects as the reference category. The vital status of 8 infants who were lost to follow-up remained unknown, and they were excluded from the analysis. The same analyses were repeated for each of the 3 mortality outcomes and for birth asphyxia after inclusion of an interaction term between treatment group and preterm birth (\( < 37 \) wk of gestation) in the model. The interaction terms were tested at the 5% significance level. All analyses were performed by using SAS version 6 (SAS Institute Inc, Cary, NC).

RESULTS

Among a total of 36,083 married women of reproductive age, 14,185 were eligible for inclusion in the routine surveillance for new pregnancies (Figure 1). Mean maternal weight, height, and body mass index (in kg/m\(^2\)) were \( \approx 44 \) kg, 150 cm, and 19, respectively, and did not differ by treatment group (20). A total of 4,998 pregnant women (\( \approx 1,000 \) per treatment arm) were enrolled in the study over a surveillance period of 1 y. Of these, 72 apparent pregnancies were excluded, including those that were false positives (\( n = 6 \)), had unknown outcomes (\( n = 3 \)), and ended as induced abortions (\( n = 63 \)). A total of 4,130 infants were born to the remaining 4,926 pregnant women, of whom all but 8 were followed until the end of the study in April 2001, which represented complete follow up of \( \approx 6 \) mo. In all, 230 infants died by 6 mo of age, and an additional 26 deaths occurred by the end of the first year.

Baseline characteristics did not differ significantly by treatment group (Table 1). Nearly one-half of all the mothers were enrolled before 9 wk of gestation, and only 8–10% were enrolled after 16 wk of gestation. The median compliance with supplementation was 86–88% during pregnancy and 70–80% in the first 12 wk postpartum (data not shown). The level of compliance did not differ across treatment groups during pregnancy but did differ slightly between the groups during the postpartum period: the median compliance in the control group was slightly lower (71%) than that in the other groups (77–80%). As reported previously (20), the RRs for low birth weight (\(< 2,500 \) g) were 1.00 (95% CI: 0.88, 1.15), 0.84 (95% CI: 0.72, 0.99), 0.96 (95% CI: 0.83, 1.11), and 0.86 (95% CI: 0.72, 0.99).
rates (data not shown). Among the infants born to mothers in the control group, the 3-mo mortality rate for the preterm infants was higher (RR: 6.3; 95% CI: 3.4, 12.1) than that for the term infants. Among the preterm births, supplementation was associated with protective RRs of 0.36 (95% CI: 0.18, 0.75) and 0.53 (95% CI: 0.30, 0.92) for the FA and FAFe groups. The protective RR estimates for the FAFeZn and MN groups had 95% CIs that included 1. Among the term births, there was no evidence of improved infant survival in any of the supplement groups. The term infants whose mothers were in the MN group appeared to have a higher risk of dying than did those whose mothers were in the control group (RR: 1.74; 95% CI: 1.00, 3.04).

The rate of neonatal death attributed to birth asphyxia was lower in the FA, FAFe, and FAFeZn groups than in the control group (Table 3). However, only the difference between the FAFeZn group (RR: 0.23; 95% CI: 0.04, 0.81) and the control group was significant.

**DISCUSSION**

We examined the survival of infants in a randomized clinical trial in which prenatal micronutrient supplementation resulted in small but significant decrements in the incidence of low birth weight but not of preterm delivery (20). Although our analysis showed consistently higher survival rates among the infants
whose mothers received folic acid with or without iron or iron + zinc than among the infants whose mothers were in the control group, we had low power (≈20%) to detect the reductions in mortality of ≈20% that were observed. In addition, multiple micronutrient supplementation, which was noted to exert the largest effect on birth weight (increase of 64 g; 95%
CI: 12.115) (20), surprisingly resulted in a survival pattern that did not differ significantly from that observed in the control group. Further analysis showed a significant interaction between treatment and preterm birth on mortality; the apparent overall reduction in mortality with folic acid and folic acid + iron was limited to the preterm infants only. Zinc appeared to attenuate the mortality reduction observed with folic acid or folic acid + iron, although the CIs in all 3 groups overlapped. A similar attenuating effect was also evident among the preterm infants in the MN group.

It is unlikely that these results were biased, because we had an extremely low rate of loss to follow-up in the study. Assuming that any posited survival benefit could not have extended beyond the supplementation period, we examined mortality differences by treatment allocation among the infants up to 3 mo of age. In addition, we observed no evidence of a reversal of treatment effects beyond 3 mo of age. There was an apparent sustained (but not additional) beneficial effect of maternal supplementation on survival from 3 to 12 mo of age, but a much smaller proportion of deaths occur in this time period than in the period from 0 to 3 mo of age.

Few studies have examined the effect of maternal nutritional interventions on fetal loss and infant mortality. One randomized controlled trial in the Gambia found that significant reductions in low birth weight and perinatal mortality were associated with consumption during pregnancy of food supplements that provided high amounts of calories and protein (28). In HIV-1–infected Tanzanian women, multivitamins (20 mg thiamine, 20 mg riboflavin, 25 mg vitamin B-6, 100 mg niacin,

### TABLE 2
Rates and relative risks (RRs) of perinatal, neonatal, and infant mortality by treatment group

<table>
<thead>
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<th>Rate/1000 live births</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perinatal deaths&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>70/916</td>
<td>76.4</td>
<td>1.00</td>
</tr>
<tr>
<td>FA</td>
<td>56/814</td>
<td>68.8</td>
<td>0.89 (0.63, 1.26)</td>
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<tr>
<td>FAFe</td>
<td>50/801</td>
<td>62.4</td>
<td>0.80 (0.55, 1.17)</td>
</tr>
<tr>
<td>FAFeZn</td>
<td>55/858</td>
<td>64.1</td>
<td>0.83 (0.57, 1.21)</td>
</tr>
<tr>
<td>MN</td>
<td>80/919</td>
<td>87.1</td>
<td>1.14 (0.82, 1.56)</td>
</tr>
<tr>
<td>Neonatal deaths&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>40/876</td>
<td>45.7</td>
<td>1.00</td>
</tr>
<tr>
<td>FA</td>
<td>28/777</td>
<td>36.0</td>
<td>0.79 (0.50, 1.26)</td>
</tr>
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<td>FAFe</td>
<td>28/772</td>
<td>36.3</td>
<td>0.80 (0.50, 1.27)</td>
</tr>
<tr>
<td>FAFeZn</td>
<td>31/827</td>
<td>37.5</td>
<td>0.82 (0.50, 1.34)</td>
</tr>
<tr>
<td>MN</td>
<td>47/870</td>
<td>54.0</td>
<td>1.19 (0.77, 1.83)</td>
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<td>Infant deaths (0–3 mo)&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>49/876</td>
<td>55.9</td>
<td>1.00</td>
</tr>
<tr>
<td>FA</td>
<td>34/777</td>
<td>43.8</td>
<td>0.78 (0.52, 1.17)</td>
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<td>0.79 (0.52, 1.20)</td>
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<td>48.4</td>
<td>0.87 (0.57, 1.31)</td>
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<tr>
<td>MN</td>
<td>52/870</td>
<td>59.8</td>
<td>1.07 (0.75, 1.58)</td>
</tr>
</tbody>
</table>

1 C, control group (received vitamin A only); FA, group who received vitamin A + folic acid; FAFe, group who received vitamin A + folic acid + iron; FAFeZn, group who received vitamin A + folic acid + iron + zinc; MN, group who received vitamin A + folic acid + iron + zinc + other micronutrients. There were no significant differences between the treatment groups.

2 Stillbirths and deaths among liveborn infants in the first 7 d of life/live births and stillbirths.

3 Deaths from 0 to 28 d of life/live births.

4 Deaths from 0 to 90 d of life/live births.
50 μg vitamin B-12, 500 mg vitamin C, 30 mg vitamin E, and 0.8 mg folic acid) given in doses that were 2–10 times the recommended dietary allowance for pregnancy led to a rate of fetal death that was 40% lower than that in the placebo group (29). However, the implications of this for uninfected populations are unclear.

It is essential to consider why maternal multiple micronutrient supplementation failed to reduce mortality to an extent similar to that observed with folic acid alone or with iron. One explanation may relate to the disproportionately higher rate of high birth weight (>3.3 kg) among the infants whose mothers received multiple micronutrients than among those whose mothers were in the control group (20), an effect that was predictably evident among the term infants only. Specifically, among term births, supplementation with multiple micronutrients (but not with other combinations of micronutrients) led to a significantly higher risk of high birth weight (RR: 1.71; 95% CI: 1.10, 2.65) than did supplementation with vitamin A alone (ie, the control treatment), and high birth weight was associated with an increased risk of symptoms of birth asphyxia (RR: 1.49; 95% CI: 1.04, 2.13). On examination, we found that the risk of symptoms of birth asphyxia was higher among the term infants whose mothers received multiple micronutrients than among those whose mothers were in the control group (Figure 4). Thus, while multiple micronutrient supplementation improved survival among the preterm infants (RR: 0.70; 95% CI: 0.41, 1.17), it also appeared to increase high

![FIGURE 4](https://academic.oup.com/ajcn/article-abstract/78/6/1194/4677532)
birth weight and the associated risk of birth asphyxia, a known cause of perinatal mortality (30), among the term infants. These countervailing influences may have cancelled one another out and thus resulted in multiple micronutrients seemingly having no overall effect on mortality (Figure 5). Other mechanisms that might also explain the lack of mortality benefit due to multiple micronutrient supplementation may exist but remain to be elucidated.

These results, coupled with the observation that folic acid appeared to reduce mortality without improving birth weight (20), suggest that improvement in mortality observed with maternal micronutrient supplementation may not always be mediated through increased birth weight. Although birth weight is commonly used as a proxy measure for potential infant health and survival, excess perinatal and neonatal mortality has been shown to operate through mechanisms other than birth weight (31–34). Indeed, health benefits have been previously described in infants after maternal micronutrient supplementation that did not result in increased birth weight. In a randomized clinical trial in Niger, supplementation with 100 mg elemental Fe had no effect on birth weight (35), and yet there was some evidence that fetal loss and neonatal death were reduced (36). In Bangladesh, the incidences of acute diarrhea, dysentery, and impetigo were significantly lower in low-birthweight infants whose mothers received zinc than in those whose mothers received placebo (37), even though birth weight itself did not differ significantly between the 2 groups of infants (16). Small size due to preterm delivery may be more strongly associated with perinatal mortality than is low birth weight per se (38, 39). In the present study, maternal supplementation with folic acid (alone or with iron) improved the survival of high-risk preterm infants even though the risk of preterm delivery itself remained unchanged (20).

Our results are likely to be applicable to poor, rural populations in south Asia, where the prevalences of maternal protein-energy malnutrition and micronutrient deficiencies are high and where the prevalence of HIV-1 infection is low. Currently, there is a move toward using multiple micronutrient supplements in pregnant women to reduce adverse pregnancy outcomes, including low birth weight and infant mortality, in the developing world. However, further understanding of the mechanisms involved and of the potential interactions that may exist among nutrients and that could produce potentially adverse outcomes is needed. The rationale for adding other micronutrients to a maternal folic acid + iron supplement to improve pregnancy outcomes should receive careful examination. This study clearly needs to be replicated in different populations to appropriately inform policies and to develop effective maternal nutrition programs in the developing world.

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PC was the principal investigator, designed the study hypothesis and protocol, directed the implementation of the study, conducted the analyses, and is the guarantor for the study. KPW provided help during the conceptual phase of the study, helped with the study procedures, and assisted in interpreting the results and writing the manuscript. SKK directed the field implementation, helped with the development of forms, and conducted the infant verbal autopsy review. SCL supervised the field procedures, data collection, and quality control and helped to design forms and procedures and to edit the manuscript. EKP helped to develop forms, manage and enter data, analyze data, and edit the manuscript. JK helped in the study design, data management procedures, data analysis, and the writing of the manuscript. SRS supervised field procedures, community preparation and advocacy, and translations of forms and manuals. AS contributed to data interpretation and manuscript editing. None of the authors had any conflicts of interest.

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