Micronutrient Supplementation and Pregnancy Outcomes

Double-Blind Randomized Controlled Trial in China

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Background: Beyond perinatal folic acid supplementation, the need for additional prenatal prophylaxis of iron with or without other micronutrients remains unclear. We aim to investigate the maternal and infant health effects of iron plus folic acid and multiple micronutrient supplements vs folic acid alone when provided to pregnant women with no or mild anemia.

Methods: In this randomized double-blind controlled trial, 18 775 nulliparous pregnant women with mild or no anemia were enrolled from 5 counties of northern China from May 2006 through April 2009. Women were randomly assigned to daily folic acid (400 μg) (control), folic acid–iron (30 mg), or folic acid, iron, and 13 additional vitamins and minerals provided before 20 weeks gestation to delivery. Primary outcome was perinatal mortality. Secondary outcomes included neonatal and infant mortality, preterm delivery, birth weight, birth length, gestational duration, and maternal hemoglobin concentration and anemia.

Results: A total of 92.7% of women consumed 80% to 100% of supplements as instructed. On average, women consumed 177 supplements. Compared with daily prenatal folic acid, supplementation with iron–folic acid with or without other micronutrients did not affect the rate of perinatal mortality (8.8, 8.7, and 8.3, respectively) per 1000 births, and relative risks (RRs) were 1.00 (95% CI, 0.68-1.46; $P = .99$) and 0.94 (95% CI, 0.64-1.39; $P = .76$), respectively. Risk of other adverse maternal and infant outcomes also did not differ, except that RRs for third-trimester maternal anemia were 0.72 (95% CI, 0.63-0.83; $P < .001$) and 0.71 (95% CI, 0.62-0.82; $P < .001$), respectively.

Conclusion: Prenatal iron–folic acid and other micronutrient supplements provided to Chinese women with no or mild anemia prevented later pregnancy anemia beyond any benefit conferred by folic acid alone but did not affect perinatal mortality or other infant outcomes.

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ABOUT 3 MILLION STILLbirths and 3 million early neonatal deaths occurred worldwide in 2004, 98% of which were in less developed countries.[1] A high perinatal mortality rate was reported in rural China in 2000.[2] Potential preventable causes of stillbirths and early neonatal deaths are maternal anemia and related micronutrient deficiencies.[3] Aside from perinatal folic acid supplements to prevent neural tube defects, multiple health organizations recommend pregnant women routinely receive iron–folic acid supplements to prevent anemia.[4] Meta-analyses of randomized controlled trials (RCTs) indicate that daily prenatal iron–folic acid supplementation prevents iron deficiency and anemia.[5,6] The effect of prenatal iron–folic acid supplementation on perinatal mortality and other maternal and infant outcomes remains unclear, particularly among nonanemic women. Thus, some question the added benefit of prophylactic iron supplementation.[7]

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In some settings, other micronutrient deficiencies may limit the effectiveness of prenatal iron–folic acid supplementation,[8,9] leading to trials to determine the maternal and infant health effects conferred from additional multiple micronutrients (MMN) vs iron–folic acid alone.[10,11] In 2005, only 2 trials of iron–folic acid vs MMN supplements had been published, but neither was adequately powered to examine perinatal morality. A study in Xian, China,[12] used cluster randomization to examine birth weight as the primary outcome; the amount of iron in the iron–folic

acid supplement was 60 mg vs 30 mg in the MMN supplement. It was unknown if this higher dose of iron would affect the comparison owing to either increased gastrointestinal effects or interactions with other nutrients. In recent meta-analyses, provision of MMN supplements vs iron–folic acid improved mean birth weight and reduced the risk of low birth weight but did not benefit birth length, head circumference, or the duration of gestation.[13,14] The effects of MMN supplements on fetal and infant deaths were inconsistent[15-22] and may have been modified by maternal baseline nutrition.[23]

China is a country in nutrition transition.[24] In China, 29% of pregnant women were anemic in 2002.[25] In southeast China, prenatal anemia prevalence declined by more than 50% between 1993 and 2005.[26] With the exception of periconceptional folic acid, prenatal iron and other micronutrients are not routinely prescribed or used by nonanemic women. Similarly, in the United States and other industrialized countries, there are conflicting recommendations about use of prophylactic iron with or without other nutrients.[7]

The objective of the current study is to investigate the maternal and infant health effects of iron–folic acid and MMN supplements vs iron–folic acid alone when provided to pregnant women with no or mild anemia. We hypothesized that prenatal iron–folic acid supplements with or without other micronutrients, given from the first prenatal visit through delivery, would reduce perinatal mortality beyond any reductions conferred by iron–folic acid alone.

METHODS

STUDY SETTING AND DESIGN

The trial took place nearby Beijing in 5 rural counties in Hebei Province, China, where basic health services were provided through 3-tier (county, township, and village) health care networks. Village clinics and township hospitals provided basic prenatal health care services, and county hospitals provided delivery service. Health facility and service capacity were similar in 5 counties, and the same guidelines or procedures for prenatal health care and delivery were used. The population at the time of the study was about 2.5 million, and gross domestic product per capita about $4700.

Eligible pregnant women were enrolled from May 2006 through April 2009 and individually randomized in a 1:1:1 ratio to receive a daily supplement containing folic acid, iron–folic acid, or MMN from early pregnancy through delivery. The study protocol was approved by the institutional review boards of the Centers for Disease Control and Prevention, Atlanta, Georgia, and Peking University, Beijing, China, and renewed annually.

PARTICIPANTS

To be eligible, pregnant women (1) recorded dates of their menstruation for 2 or more months before they became pregnant, (2) were nulliparous, (3) were at least 20 years old, (4) were not more than 20 weeks gestation, (5) were legally competent, (6) had not consumed micronutrient supplements other than folic acid in the prior 6 months, (7) had a hemoglobin (Hb) level greater than 10.0 g/dL, (8) resided in and received prenatal care in 1 of 5 counties, and (9) consented to participate. (To convert Hb to grams per liter, multiply by 10.0.)

ENROLLMENT AND INFORMED CONSENT

Before the study started, the project was publicized in each participating county using pamphlets, posters, radio, and television. During the first prenatal visit, the consent form was read to each woman by a physician trained in informed consent procedures. After the woman provided verbal consent, the form was signed by the physician plus a witness.

RANDOMIZATION AND MASKING

Randomization was stratified by county, and random block sizes of 3, 6, and 9 were used to ensure geographical balance with an approximately equal distribution of treatments within and across study counties. A statistician external to the study randomly assigned ten 4-digit lot numbers to each of the 3 supplement types (masked to the formulation and allocation) and generated the assignment list for each county proportional to the expected number of participants; within each county and block, lot numbers were randomly assigned using RANUNI in SAS statistics software (SAS Institute Inc). Aside from a pharmaceutical engineer who ensured allocation of lot numbers to the correct supplement formulations, all others (ie, participants, local physicians, study personnel, and investigators) were masked to the identity of the supplements. Treatment codes were broken after completion of the study and main analyses.

INTERVENTION

At enrollment, the physician assigned women the next lot number on the randomization schedule. Each woman received 2 bottles of supplements at enrollment and 1 at monthly follow-up visits. Each bottle contained 31 supplements, including 1 of the supplements (see eMethods 1 for supplement formulations; http://www.jamainternalmed.com) according to lot number. The capsules were of the same size, color, and shape, and bottles were identical except for the lot number. Study participants were instructed to take 1 supplement daily from enrollment until delivery. Supplements were provided at no cost; otherwise, no compensation was given for participation.

STUDY OUTCOMES

Trained county or township physicians completed relevant measurements and collected data based on a perinatal and child health care surveillance system (see eMethods 2 for detailed data collection procedures). To ensure data quality, Peking University staff conducted various training programs, performed monthly site supervisions, and cross-checked all death events. The primary outcome was perinatal mortality. Secondary outcomes included neonatal deaths, infant deaths, maternal Hb concentration and anemia at 24 to 28 weeks of gestation, birth weight, birth length, duration of gestation, and preterm delivery. (Outcome definitions are provided in eMethods 3.)

SAMPLE SIZE

The estimated perinatal mortality rate was 16 per 1000 births in the folic acid group based on our previous study.[27] A 40% reduction in the iron–folic acid group compared with the folic acid group and a 50% reduction in the MMN group were hypothesized based on various observational studies.[28-32] With a 2-sided significance level of $P = .05$, β-error specification of 0.20, and correction for continuity, 5272 per group were needed to detect a 40% reduction in the iron–folic acid group compared with the folic acid group and a 50% reduction in the MMN group compared with the iron–folic acid group. To account for the estimated 4.7% of women lost to

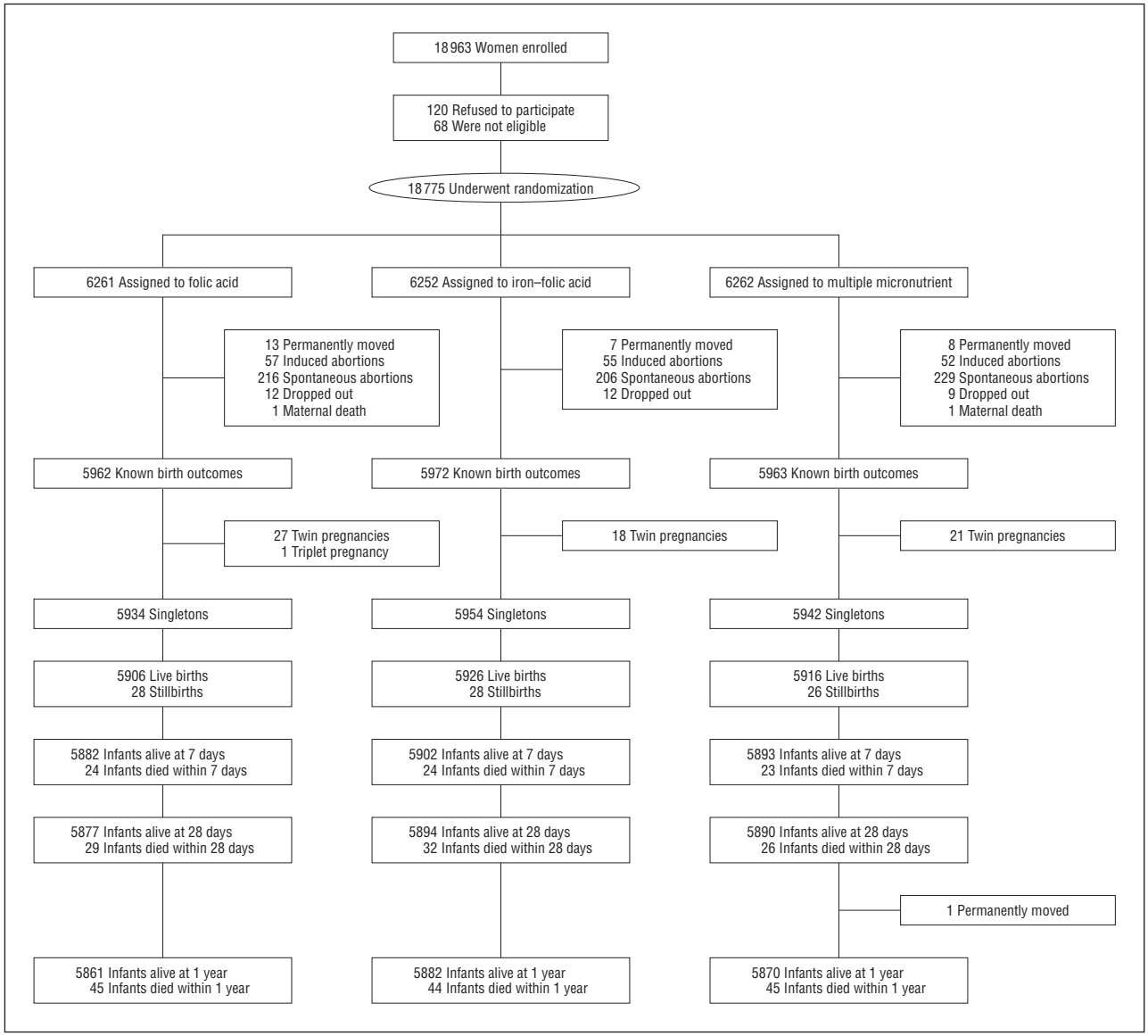

Figure. Flowchart of participants.

follow-up, 4.2% of dropouts, and 4.0% of nonadherence,[27] 6280 women per group were needed. The statistical power was expected to be adequate for outcomes with a higher baseline prevalence (ie, low birth weight, preterm birth, and maternal anemia).

STATISTICAL ANALYSES

Multiple pregnancies were excluded from analyses. The denominator for perinatal mortality was live births plus stillbirths. The denominator for other study outcomes was live births. We defined mean compliance as the number of supplements consumed divided by the number of days from enrollment to birth; the number of supplements consumed was estimated from the number of supplements remaining in the bottle at each return visit.

All analyses were based on an intent-to-treat principle. All randomized women with a known birth outcome were included in analyses irrespective of compliance. We examined the distribution of key baseline characteristics among the 3 groups using χ^2 tests for categorical variables and analysis of variance for continuous. χ^2 Tests and independent sample *t* tests were used to test the differences in dichotomous and continuous outcomes between supplement groups (iron–folic acid vs folic acid, MMN vs folic acid, and MMN vs iron–folic acid), respectively. Unadjusted relative risks (RRs) with 95% confidence intervals (CIs) were calculated for mortality, low birth weight, preterm birth, and maternal anemia. Rate differences with 95% CIs were also calculated for mortality; a number needed to treat with 95% CIs was calculated for outcomes with statistical significance. Unadjusted mean differences with 95% CIs were calculated for continuous outcomes. The Data Safety Monitoring Board met 4 times during the study and reviewed 3 interim analyses by supplement group masked to allocation, in which the significance levels began lower and ended at the final analysis close to the prespecified overall significance level.[33] All *P* values were 2-sided, and statistical significance was set at $P = .05$ for the final analysis without adjustment for multiple comparisons. We used SAS statistical software (version 9; SAS Institute Inc) for all analyses.

RESULTS

Among the 18 963 pregnant women considered for enrollment, 120 refused to participate in the study, and 68 were

Table 1. Baseline Maternal Characteristics at Enrollment According to Study Intervention[a]

Characteristic	Group, No. (%) FA (n = 6261)	IFA (n = 6252)	MMN (n = 6262)
Maternal age, mean (SD), y	23.7 (2.9)	23.7 (2.9)	23.6 (2.8)
Education			
≤Primary	94 (1.5)	110 (1.8)	94 (1.5)
Secondary	5011 (80.0)	5017 (80.2)	5025 (80.2)
≥High school	1156 (18.5)	1125 (18.0)	1143 (18.3)
Ethnicity			
Han	6180 (98.7)	6184 (98.9)	6192 (98.9)
Other	81 (1.3)	68 (1.1)	70 (1.1)
Occupation			
Farmer	5674 (90.6)	5691 (91.0)	5682 (90.7)
Other	587 (9.4)	561 (9.0)	580 (9.3)
BMI			
<18.5	365 (5.8)	371 (5.9)	364 (5.8)
18.5-24.9	5008 (80.0)	5029 (80.4)	5009 (80.0)
25.0-29.9	759 (12.1)	735 (11.8)	762 (12.2)
≥30.0	129 (2.1)	117 (1.9)	127 (2.0)
Height, mean (SD), cm	160.1 (4.5)	160.2 (4.5)	160.2 (4.5)
Gestational week			
<12	3359 (53.6)	3317 (53.1)	3364 (53.7)
≥12	2902 (46.4)	2935 (46.9)	2898 (46.3)
Gestational week, mean (SD)	11.9 (4.6)	12.0 (4.5)	11.9 (4.6)
Hemoglobin level, g/dL			
10.0-10.9	369 (5.9)	374 (6.0)	317 (5.1)
11.0-11.9	1408 (22.5)	1457 (23.3)	1433 (22.9)
12.0-12.9	2640 (42.2)	2628 (42.0)	2662 (42.5)
≥13.0	1844 (29.4)	1793 (28.7)	1850 (29.5)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); FA, folic acid; IFA, iron–folic acid; MMN, multiple micronutrient.

SI conversion factor: To convert hemoglobin to grams per liter, multiply by 10.

[a] Data are expressed as number (percentage) of participants except where noted. χ^2 Tests were used to examine statistical differences in categorical variables and analysis of variance to examine differences in means. $P > .05$ for all comparisons.

Table 2. Compliance and Number of Supplement Consumed According to Study Intervention[a]

Compliance and Distribution	Group, No. (%) FA (n = 5934)	IFA (n = 5954)	MMN (n = 5942)
Mean compliance, %	93.3 (12.6)	92.8 (13.3)	91.5 (16.0)
Compliance distribution, %			
0-19	54 (0.9)	64 (1.1)	108 (1.8)
20-39	46 (0.8)	49 (0.8)	71 (1.2)
40-59	67 (1.1)	66 (1.1)	94 (1.6)
60-79	201 (3.4)	226 (3.8)	252 (4.2)
80-100	5566 (93.8)	5549 (93.2)	5417 (91.2)
Supplement (capsules) consumed, mean (SD), No.	179 (41)	177 (42)	176 (45)
Supplement (capsules) consumed, range			
<90	152 (2.6)	179 (3.0)	253 (4.3)
90-119	256 (4.3)	243 (4.1)	284 (4.8)
120-149	941 (15.9)	990 (16.6)	976 (16.4)
150-179	1388 (23.4)	1409 (23.7)	1306 (22.0)
≥180	3197 (53.9)	3133 (52.6)	3123 (52.6)

Abbreviations: FA, folic acid; IFA, iron–folic acid; MMN, multiple micronutrient.

[a] Data are expressed as number (percentage) of participants except where noted. Compliance calculated by number of actual supplements consumed divided by number of supplements expected to be consumed.

not eligible (**Figure**). Of the 18 775 women randomized, 28 moved, 33 dropped out, 2 died during pregnancy (1 from a traffic accident and 1 from autoimmune disease), and 815 had spontaneous or induced abortions. Of the 17 897 remaining women with known pregnancy outcomes (95.3%), 17 830 women (99.6%) had singleton pregnancies; 17 748 ended their pregnancy with live births, 82 with stillbirths. Among the live births, 71 early neonatal deaths, 87 neonatal deaths, and 134 infant deaths were identified. Of the 87 neonatal deaths, 24 died of asphyxia, 23 of premature birth, 15 had birth defects, 9 had pneumonia, and 16 died of other or unknown causes. The number of women having multiple pregnancies were not statistically different across the treatment groups (P=.30) (Figure).

The baseline characteristics were balanced across supplement groups (**Table 1**). The mean (SD) maternal age, gestation at enrollment, and Hb level were 23.7 (2.9) years, 11.9 (4.6) weeks, and 12.5 (1.0) g/dL, respectively. Almost all participants were of Han ethnicity, 1.6% had primary or less education, and 90.8% were farmers. About 5% to 6% of women had Hb concentrations of 10.0 to 10.9 g/dL.

Adherence to the assigned supplements was high, and only 20 women reported having taken additional micronutrient supplements including calcium, iron, zinc, or MMNs. A total of 92.7% women consumed 80% to 100% of supplements as instructed; the mean number of supplements consumed was 177 capsules (**Table 2**). No serious adverse effects were reported. The adverse effects were nausea, vomiting, or other mild gastrointestinal discomfort: 133 women in the folic acid group (2.2%) reported gastrointestinal discomfort, 212 (3.6%) in the iron–folic acid group, and 355 (6.0%) in the MMN group ($P < .001$).

The perinatal mortality rate was 8.76 of 1000 births for the folic acid group, 8.73 of 1000 for the iron–folic acid group, and 8.25 of 1000 for the MMN group. Compared with prenatal folic acid alone, neither iron–folic acid (RR, 1.00; 95% CI, 0.68-1.46; P = .99) nor MMN supplements (RR, 0.94; 95% CI, 0.64-1.39; P = .76) affected the risk of perinatal mortality (**Table 3**). Compared with iron–folic acid, MMN did not affect the risk of perinatal mortality (RR, 0.94; 95% CI, 0.64-1.39; P = .77). Similarly, risk of stillbirths, early neonatal deaths, neonatal deaths, or infant deaths did not differ by supplement group.

Compared with folic acid alone, iron–folic acid and MMN increased third-trimester maternal Hb concentration by 0.04 and 0.06 g/dL, respectively, and decreased the anemia prevalence by 28% and 29% (**Table 4**), respectively, with a number needed to treat of 47 (95% CI, 33-81) for the iron–folic acid group and 46 (95% CI, 32-77) for the MMN group. Neither gestation duration nor birth weight or length differed significantly by supplement group.

COMMENT

In this primarily nonanemic rural population, prenatal supplementation with iron–folic acid or MMN vs folic acid alone did not decrease the risk of perinatal mortality or other

Table 3. Perinatal Deaths, Stillbirths, and Neonatal and Infant Deaths[a]

Outcomes	No./No. (Cases/1 000)			IFA vs FA		MMN vs FA		MMN vs IFA	
	FA	IFA	MMN	RR (95% CI)	RD (95% CI)	RR (95% CI)	RD (95% CI)	RR (95% CI)	RD (95% CI)
Perinatal death[b]	52/5934 (8.76)	52/5954 (8.73)	49/5942 (8.25)	1.00 (0.68 to 1.46)	0.02 (−0.03 to 0.03)	0.94 (0.64 to 1.39)	0.02 (−0.04 to 0.03)	0.94 (0.64 to 1.39)	0.02 (−0.04 to 0.03)
Stillbirth[c]	28/5934 (4.72)	28/5954 (4.70)	26/5942 (4.38)	1.00 (0.59 to 1.68)	0.01 (−0.03 to 0.02)	0.93 (0.54 to 1.58)	0.01 (−0.03 to 0.02)	0.93 (0.55 to 1.58)	0.01 (−0.03 to 0.02)
Early neonatal death[d]	24/5906 (4.06)	24/5926 (4.05)	23/5916 (3.89)	1.00 (0.57 to 1.75)	0.01 (−0.02 to 0.02)	0.96 (0.54 to 1.69)	0.01 (−0.02 to 0.02)	0.96 (0.54 to 1.70)	0.01 (−0.02 to 0.02)
Neonatal death[e]	29/5906 (4.91)	32/5926 (5.40)	26/5916 (4.39)	1.10 (0.67 to 1.82)	0.01 (−0.02 to 0.03)	0.90 (0.53 to 1.52)	0.01 (−0.03 to 0.02)	0.81 (0.49 to 1.36)	0.01 (−0.04 to 0.02)
Infant death[f]	45/5906 (7.62)	44/5926 (7.42)	45/5915 (7.61)	0.97 (0.64 to 1.48)	0.02 (−0.03 to 0.03)	1.00 (0.66 to 1.50)	0.02 (−0.03 to 0.03)	1.02 (0.68 to 1.55)	0.02 (−0.03 to 0.03)

Abbreviations: FA, folic acid; IFA, iron–folic acid; MMN, multiple micronutrient; RD, risk difference; RR, relative risk.
[a] χ^2 Tests were used to examine statistical differences in death rates between each of the 2 groups. $P > .05$ for all comparisons.
[b] Stillbirth and early neonatal death. Perinatal death is primary outcome.
[c] From 28 weeks of gestation to delivery.
[d] From birth to 6 days after delivery.
[e] From birth to 28 days after delivery.
[f] During the first year of life.

Table 4. Birth Outcomes and Maternal Hemoglobin Level in the Study Groups[a]

Outcome	FA (n = 6261)	IFA (n = 6252)	MMN (n = 6262)	IFA vs FA		MMN vs FA		MMN vs IFA	
				MD/RR (95% CI)	*P* Value	MD/RR (95% CI)	*P* Value	MD/RR (95% CI)	*P* Value
Birth weight, g									
Infants, No.	5905	5922	5913						
Mean (SD)	3290.6 (391.5)	3292.5 (389.0)	3299.0 (392.4)	1.91 (−12.16 to 15.98)	.79	8.34 (−5.79 to 22.48)	.25	6.43 (−7.65 to 20.51)	.37
Low birth weight, <2500 g	125 (2.1)	129 (2.2)	116 (2.0)	1.03 (0.81 to 1.31)	.82	0.93 (0.72 to 1.19)	.55	0.90 (0.70 to 1.15)	.10
Birth length, cm									
Infants, No.	5905	5922	5913						
Mean (SD)	50.0 (1.1)	50.0 (1.1)	50.0 (1.0)	0.01 (−0.03 to 0.05)	.60	0.03 (−0.01 to 0.07)	.14	0.02 (−0.02 to 0.06)	.34
Gestational age, wk									
Infants, No.	5906	5926	5916						
Mean (SD)	39.6 (1.7)	39.6 (1.7)	39.6 (1.6)	−0.03 (−0.09 to 0.03)	.35	0.02 (−0.04 to 0.09)	.43	0.05 (−0.01 to 0.11)	.08
Preterm birth, <37 wk	353 (6.0)	340 (5.7)	308 (5.2)	0.96 (0.83 to 1.11)	.58	0.87 (0.75 to 1.01)	.07	0.91 (0.78 to 1.05)	.20
Maternal Hb level at 24-28 wk of gestation									
Women, No.	5896	5913	5904						
Hb level, g/dL	12.2 (0.9)	12.2 (0.9)	12.3 (0.9)	0.04 (0.01 to 0.07)	.01	0.06 (0.03 to 0.09)	<.001	0.02 (−0.02 to 0.05)	.34
Anemia, Hb level <11.0g/dL	452 (7.7)	327 (5.5)	323 (5.5)	0.72 (0.63 to 0.83)	<.001	0.71 (0.62 to 0.82)	<.001	0.99 (0.85 to 1.15)	.89

Abbreviations: FA, folic acid; IFA, iron–folic acid; Hb, hemoglobin; MD, mean difference; MMN, multiple micronutrient; RR, relative risk.
SI conversion factor: To convert hemoglobin to grams per liter, multiply by 10.
[a] Data are expressed as number (percentage) of participants or mean (SD) unless otherwise indicated. *P* values were calculated based on χ^2 tests or independent sample *t* tests as appropriate.

infant or maternal outcomes except maternal anemia. Compared with folic acid alone, iron–folic acid and MMN increased Hb concentration and reduced anemia by about 30%. Our study population was rural (91% were farmers); nearly all women had at least a secondary education, and few were undernourished or anemic. In addition, having monitored their menstrual cycle for 2 or more months before enrollment, women were cognizant of their last menstrual period and prenatal health. Once enrolled, women were followed monthly and delivered in the hospital. The lack of differences in infant outcomes with prenatal supplementation may underline the importance of secondary factors, such as nutritional status, prenatal care, and economic status in assessing the degree to which our findings can be generalized.

Our findings are consistent with 2 previous meta-analyses of RCTs in developing countries comparing the effects of iron–folic acid with MMN on neonatal and perinatal mortality.[34,35] Unlike one meta-analysis[36] that found a trend toward higher early neonatal mortality in the group receiving MMN vs iron–folic acid alone, we found no difference between these groups. A recent meta-analysis[34] showed an increased risk of neonatal mortality with MMN compared with iron–folic acid in settings where less than 60% of births occurred in facilities; however, consistent with our trial, there was no increased risk in settings where most births occurred in facilities. Thus, our results should be interpreted in the context of the existing burden of micronutrient deficiencies, adverse pregnancy, and fetal outcomes, and the setting. Our study population had

low prevalence rates of all the outcomes assessed in the study, including a low prevalence of anemia (5%-7%) in late pregnancy and a low birth weight prevalence (approximately 2%), which were even lower than those seen in many industrialized countries. At such low rates of adverse outcomes, it is not surprising that the intervention had no impact. As such, this trial is not comparable with many of the studies included in the meta-analyses. Unlike many trials conducted in poor populations in developing countries, our trial is generalizable to a well-nourished population of nonanemic or mildly anemic women with good access to health care.

In this primarily nonanemic population, the relative reduction of anemia (approximately 30%) was substantial. Although iron status was not assessed in the entire population, this reduction suggests about 30% of anemia was due to iron deficiency, and only one-third of anemic women in our population could be expected to respond to iron supplementation. Anemic women are likely to be iron deficient and would benefit from supplements containing iron. However, overall improvement in Hb concentration was limited, owing to low anemia prevalence at baseline (<6%). Because 21.7% of the population had high Hb levels (≥13.2 g/dL)[37,38] at enrollment and high Hb level has been hypothesized as a risk factor, we conducted post hoc analyses to test for possible interaction between supplement groups and maternal baseline Hb status (<13.2 g/dL vs ≥13.2 g/dL) on perinatal mortality by using Breslow-Day tests. All *P* values for interaction tests were not significant ($P > .90$).

Although we did not find a significant difference in low birth weight with prenatal MMN vs iron–folic acid supplementation, the point estimate (10% reduction) was similar to that estimated (11%-14%) in the previous meta-analyses.[13,35] In our study population, we excluded women with moderate anemia at enrollment, and the low birth weight incidence was smaller than that observed in previous studies, diminishing the possibility of observing a significant effect. Our findings with regard to the effect of iron differ with those of 2 trials conducted in the United States. One trial compared the effects of iron alone vs placebo and the other compared prenatal vitamins with and without iron, both in iron-replete, nonanemic pregnant women.[39,40] In both US trials, the iron-supplemented group had a significantly higher mean birth weight compared with the control group; the trial comparing iron with placebo showed a significantly lower incidence of infants with low birth weight[39] and increased gestational age at delivery. Although it is difficult to compare these trials owing to differences in the populations and control supplements, the low birth weight incidence among the control groups in the US studies (9.5%-16.7%) was much higher than our study (approximately 2%).

The inconsistent results between our study and those of other studies may relate to the modifying effects of maternal socioeconomic and nutritional status in response to micronutrient supplementation. In an RCT in rural western China,[41] effects of micronutrient supplementation were observed in the poorest one-third of households but not in wealthier households. Compared with folic acid alone, women from the poorest households who received iron–folic acid had significant reductions in both preterm birth and early neonatal mortality; women who received MMN had a significant reduction in preterm births and low birth weight. In the large-scale SUMMIT trial in Indonesia,[22] effects on early infant mortality (0-90 days) were observed among undernourished or anemic women; compared with women receiving iron–folic acid, women who received MMN showed significant reductions in early infant mortality (25% in undernourished women and 38% in anemic women, respectively).

Aside from the lack of a placebo group and information on the micronutrient status, the major limitation of the study was that the actual power was not adequate to detect a difference in perinatal mortality by supplement group, primarily because the observed perinatal mortality rate dramatically decreased during the past decade with the rapid socioeconomic development in China. Although there were no evident differences in perinatal mortality, we cannot rule out small differences because of inadequate sample size. Our study has several strengths. Supplements were randomized by individual. Capsule-taking was confirmed by independent household visits, and the compliance was greater than 90%. All pregnancy outcomes, including stillbirths, abortions, and early neonatal deaths, were ascertained by active community surveillance, review of vital registration certificates, and review of hospital records. Assessment of birth weight was conducted using standardized and accurate equipment and trained staff. Finally, less than 1% of those enrolled were lost to follow-up.

In summary, our study is, to our knowledge, the first large-scale, double-blind, individual RCT to directly assess the impact of prenatal supplementation on perinatal mortality in a well-nourished Chinese population with good access to health care. Given perinatal and infant mortality were similar across supplement groups, the slight improvement in Hb status with iron–folic acid and MMN supplements among nonanemic or mildly anemic women provides some limited additional support for prophylactic iron supplementation to prevent third-trimester maternal anemia.

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REFERENCES

1. World Health Organization. Neonatal and perinatal mortality: country, regional and global estimates 2004. http://whqlibdoc.who.int/publications/2007/9789241596145_eng.pdf. Accessed December 30, 2010.
2. Wu Z, Viisainen K, Wang Y, Hemminki E. Perinatal mortality in rural China: retrospective cohort study. *BMJ*. 2003;327(7427):1319.
3. Black RE, Allen LH, Bhutta ZA, et al; Maternal and Child Undernutrition Study Group. Maternal and child undernutrition: global and regional exposures and health consequences. *Lancet*. 2008;371(9608):243-260.
4. International Nutritional Anemia Consultative Group. Guidelines for the use of iron supplements to prevent and treat iron deficiency anemia. http://www.who.int/nutrition/publications/micronutrients/anaemia_iron_deficiency/1-57881-020-5/en/index.html. Accessed January 25, 2011.
5. Pena-Rosas JP, Viteri FE. Effects of routine oral iron supplementation with or without folic acid for women during pregnancy. *Cochrane Database Syst Rev*. 2006;(3):CD004736.
6. Peña-Rosas JP, Viteri FE. Effects and safety of preventive oral iron or iron + folic acid supplementation for women during pregnancy. *Cochrane Database Syst Rev*. 2009;(4):CD004736.
7. US Preventive Services Task Force. Routine iron supplementation during pregnancy. Policy statement. *JAMA*. 1993;270(23):2846-2848.
8. Shrimpton R, Shrimpton R, Schultink W. Can supplements help meet the micronutrient needs of the developing world? *Proc Nutr Soc*. 2002;61(2):223-229.
9. Sloan NL, Jordan E, Winikoff B. Effects of iron supplementation on maternal hematologic status in pregnancy. *Am J Public Health*. 2002;92(2):288-293.
10. UNICEF/UNU/WHO Study Team. *Multiple Micronutrient Supplementation During Pregnancy (MMSDP): Efficacy Trials*. London, England: Institute of Child Health, UCL; 2002.
11. UNICEF/UNU/WHO Study Team. *Composition of Multiple Micronutrient Supplement to be Used in Pilot Programmes Among Pregnant Women in Developing Countries: Report of a Workshop Held at UNICEF Headquarters*. New York, NY: UNICEF.
12. Zeng L, Dibley MJ, Cheng Y, et al. Impact of micronutrient supplementation during pregnancy on birth weight, duration of gestation, and perinatal mortality in rural western China: double blind cluster randomised controlled trial. *BMJ*. 2008;337:a2001.
13. Fall CH, Fisher DJ, Osmond C, Margetts BM; Maternal Micronutrient Supplementation Study Group. Multiple micronutrient supplementation during pregnancy in low-income countries: a meta-analysis of effects on birth size and length of gestation. *Food Nutr Bull*. 2009;30(4)(suppl):S533-S546.
14. Shah PS, Ohlsson A; Knowledge Synthesis Group on Determinants of Low Birth Weight and Preterm Births. Effects of prenatal multimicronutrient supplementation on pregnancy outcomes: a meta-analysis. *CMAJ*. 2009;180(12):E99-E108.
15. Christian P, Osrin D, Manandhar DS, Khatry SK, de L Costello AM, West KP Jr. Antenatal micronutrient supplements in Nepal. *Lancet*. 2005;366(9487):711-712.
16. Christian P, West KP, Khatry SK, et al. Effects of maternal micronutrient supplementation on fetal loss and infant mortality: a cluster-randomized trial in Nepal. *Am J Clin Nutr*. 2003;78(6):1194-1202.
17. Czeizel AE, Dudás I, Métneki J. Pregnancy outcomes in a randomised controlled trial of periconceptional multivitamin supplementation: final report. *Arch Gynecol Obstet*. 1994;255(3):131-139.
18. Fawzi WW, Msamanga GI, Spiegelman D, et al. Randomised trial of effects of vitamin supplements on pregnancy outcomes and T cell counts in HIV-1-infected women in Tanzania. *Lancet*. 1998;351(9114):1477-1482.
19. Fawzi WW, Msamanga GI, Urassa W, et al. Vitamins and perinatal outcomes among HIV-negative women in Tanzania. *N Engl J Med*. 2007;356(14):1423-1431.
20. Kaestel P, Michaelsen KF, Aaby P, Friis H. Effects of prenatal multimicronutrient supplements on birth weight and perinatal mortality: a randomised, controlled trial in Guinea-Bissau. *Eur J Clin Nutr*. 2005;59(9):1081-1089.
21. Roberfroid D, Huybregts L, Lanou H, et al; MISAME Study Group. Effects of maternal multiple micronutrient supplementation on fetal growth: a double-blind randomized controlled trial in rural Burkina Faso. *Am J Clin Nutr*. 2008;88(5):1330-1340.
22. Shankar AH, Jahari AB, Sebayang SK, et al; Supplementation With Multiple Micronutrients Intervention Trial (SUMMIT) Study Group. Effect of maternal multiple micronutrient supplementation on fetal loss and infant death in Indonesia: a double-blind cluster-randomised trial. *Lancet*. 2008;371(9608):215-227.
23. Abu-Saad K, Fraser D. Maternal nutrition and birth outcomes. *Epidemiol Rev*. 2010;32(1):5-25.
24. Zhai F, Wang H, Du S, et al. Prospective study on nutrition transition in China. *Nutr Rev*. 2009;67(suppl 1):S56-S61.
25. World Health Organization. Worldwide prevalence of anaemia 1993-2005: WHO Global Database on Anaemia. http://whqlibdoc.who.int/publications/2008/9789241596657_eng.pdf. Accessed October 30, 2011.
26. Jin L, Yeung LF, Cogswell ME, et al. Prevalence of anaemia among pregnant women in South-East China, 1993-2005. *Public Health Nutr*. 2010;13(10):1511-1518.
27. Berry RJ, Li Z, Erickson JD, et al. Prevention of neural-tube defects with folic acid in China: China-US Collaborative Project for Neural Tube Defect Prevention. *N Engl J Med*. 1999;341(20):1485-1490.
28. Garn SM, Ridella SA, Petzold AS, Falkner F. Maternal hematologic levels and pregnancy outcomes. *Semin Perinatol*. 1981;5(2):155-162.
29. Lister UG, Rossiter CE, Chong H. Perinatal mortality. *BJOG*. 1985;92(suppl s5):86-99.
30. Malhotra M, Sharma JB, Batra S, Sharma S, Murthy NS, Arora R. Maternal and perinatal outcome in varying degrees of anemia. *Int J Gynaecol Obstet*. 2002;79(2):93-100.
31. Stephansson O, Dickman PW, Johansson A, Cnattingius S. Maternal hemoglobin concentration during pregnancy and risk of stillbirth. *JAMA*. 2000;284(20):2611-2617.
32. Xiong X, Buekens P, Alexander S, Demianczuk N, Wollast E. Anemia during pregnancy and birth outcome: a meta-analysis. *Am J Perinatol*. 2000;17(3):137-146.
33. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics*. 1979;35(3):549-556.
34. Haider BA, Yakoob MY, Bhutta ZA. Effect of multiple micronutrient supplementation during pregnancy on maternal and birth outcomes. *BMC Public Health*. 2011;11(suppl 3):S19.
35. Kawai K, Spiegelman D, Shankar AH, Fawzi WW. Maternal multiple micronutrient supplementation and pregnancy outcomes in developing countries: meta-analysis and meta-regression. *Bull World Health Organ*. 2011;89(6):402-411B.
36. Ronsmans C, Fisher DJ, Osmond C, Margetts BM, Fall CH; Maternal Micronutrient Supplementation Study Group. Multiple micronutrient supplementation during pregnancy in low-income countries: a meta-analysis of effects on stillbirths and on early and late neonatal mortality. *Food Nutr Bull*. 2009;30(4)(suppl):S547-S555.
37. Murphy JF, O'Riordan J, Newcombe RG, Coles EC, Pearson JF. Relation of haemoglobin levels in first and second trimesters to outcome of pregnancy. *Lancet*. 1986;1(8488):992-995.
38. Ziaei S, Norrozi M, Faghihzadeh S, Jafarbegloo E. A randomised placebo-controlled trial to determine the effect of iron supplementation on pregnancy outcome in pregnant women with haemoglobin ≥ 13.2 g/dl [published correction appears in *BJOG*. 2007;114(10):1311]. *BJOG*. 2007;114(6):684-688.
39. Cogswell ME, Parvanta I, Ickes L, Yip R, Brittenham GM. Iron supplementation during pregnancy, anemia, and birth weight: a randomized controlled trial. *Am J Clin Nutr*. 2003;78(4):773-781.
40. Siega-Riz AM, Hartzema AG, Turnbull C, Thorp J, McDonald T, Cogswell ME. The effects of prophylactic iron given in prenatal supplements on iron status and birth outcomes: a randomized controlled trial. *Am J Obstet Gynecol*. 2006;194(2):512-519.
41. Zeng L, Yan H, Cheng Y, Dibley MJ. Modifying effects of wealth on the response to nutrient supplementation in pregnancy on birth weight, duration of gestation and perinatal mortality in rural western China: double-blind cluster randomized controlled trial. *Int J Epidemiol*. 2011;40(2):350-362.