

Effects of Prenatal Micronutrient and Early Food Supplementation on Maternal Hemoglobin, Birth Weight, and Infant Mortality Among Children in Bangladesh

The MINIMat Randomized Trial

Lars Åke Persson, MD, PhD

Shams Arifeen, MD, PhD

Eva-Charlotte Ekström, PhD

Kathleen M. Rasmussen, ScD

Edward A. Frongillo, PhD

Md Yunus, MD

for the MINIMat Study Team

MATERNAL AND CHILD UNDERNUTRITION is estimated to be the underlying cause of 3.5 million annual deaths and 35% of the total disease burden in children younger than 5 years.¹ The potential long-term consequences of nutritional imbalance or insult in fetal or early life also include cognitive impairment² and chronic diseases in adulthood.³ Effective child nutrition interventions are available to reduce stunting, prevent consequences of micronutrient deficiencies, and improve survival.⁴ The knowledge base is weaker regarding prenatal nutrition interventions of benefit for mother and offspring. Supplementation with balanced protein-energy supplements in low-income countries has resulted in increased birth weight, especially in periods of food insecurity.^{5,6} A recent meta-analysis⁷ of balanced protein-energy supplementation to pregnant women estimated a mean effect on birth weight of 60 g (95% CI, 33-87 g). Recent meta-analyses of prenatal multiple micronutrient trials have demonstrated small increases in birth weight

For editorial comment see p 2094.

Context Nutritional insult in fetal life and small size at birth are common in low-income countries and are associated with serious health consequences.

Objectives To test the hypothesis that prenatal multiple micronutrient supplementation (MMS) and an early invitation to food supplementation would increase maternal hemoglobin level and birth weight and decrease infant mortality, and to assess whether a combination of these interventions would further enhance these outcomes.

Design, Setting, and Participants A randomized trial with a factorial design in Matlab, Bangladesh, of 4436 pregnant women, recruited between November 11, 2001, and October 30, 2003, with follow-up until June 23, 2009.

Interventions Participants were randomized into 6 groups; a double-masked supplementation with capsules of 30 mg of iron and 400 µg of folic acid, 60 mg of iron and 400 µg of folic acid, or MMS containing a daily allowance of 15 micronutrients, including 30 mg of iron and 400 µg of folic acid, was combined with food supplementation (608 kcal 6 days per week) randomized to either early invitation (9 weeks' gestation) or usual invitation (20 weeks' gestation).

Main Outcome Measures Maternal hemoglobin level at 30 weeks' gestation, birth weight, and infant mortality. Under 5-year mortality was also assessed.

Results Adjusted maternal hemoglobin level at 30 weeks' gestation was 115.0 g/L (95% CI, 114.4-115.5 g/L), with no significant differences among micronutrient groups. Mean maternal hemoglobin level was lower in the early vs usual invitation groups (114.5 vs 115.4 g/L; difference, -0.9 g/L; 95% CI, -1.7 to -0.1; $P = .04$). There were 3625 live births out of 4436 pregnancies. Mean birth weight among 3267 singletons was 2694 g (95% CI, 2680-2708 g), with no significant differences among groups. The early invitation with MMS group had an infant mortality rate of 16.8 per 1000 live births vs 44.1 per 1000 live births for usual invitation with 60 mg of iron and 400 µg of folic acid (hazard ratio [HR], 0.38; 95% CI, 0.18-0.78). Early invitation with MMS group had an under 5-year mortality rate of 18 per 1000 live births (54 per 1000 live births for usual invitation with 60 mg of iron and 400 µg of folic acid; HR, 0.34; 95% CI, 0.18-0.65). Usual invitation with MMS group had the highest incidence of spontaneous abortions and the highest infant mortality rate.

Conclusion Among pregnant women in poor communities in Bangladesh, treatment with multiple micronutrients, including iron and folic acid combined with early food supplementation, vs a standard program that included treatment with iron and folic acid and usual food supplementation, resulted in decreased childhood mortality.

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in comparison with iron-folic acid supplementation alone,^{8,9} and a small reduction in the occurrence of small-for-gestational-age outcomes,¹⁰ but no reduction in risk of stillbirth, perina-

Author Affiliations and the MINIMat Study Team are listed at the end of this article.

Corresponding Author: Lars Åke Persson, MD, PhD, Department of Women's and Children's Health, International Maternal and Child Health, University Hospital, SE-751 85 Uppsala, Sweden (lars-ake.persson@kbh.uu.se).

tal mortality, or neonatal mortality.¹¹ A pooled analysis of data from trials with prenatal multiple micronutrients vs iron-folate supplements showed no difference in effect on maternal hemoglobin level or anemia.¹²

Most food supplementation programs reach pregnant women beginning in mid-pregnancy,⁷ partly because some women do not seek prenatal care in early pregnancy and because of a belief that food supplementation is likely to have the greatest effect when the fetus is growing most rapidly, during the last trimester. Variations in birth weight, however, may be determined at least partly by growth during the first trimester.¹³ Although studies are limited, there are reasons to believe that a healthy diet from early pregnancy with sufficient intake of macronutrients and micronutrients is important for the prevention of several adverse pregnancy outcomes.¹⁴⁻¹⁶

The proportion of malnourished mothers and children remains high in many areas of the world, especially in South Asia, where more than one-quarter of newborns have a low weight.¹⁷ In different studies in urban and rural Bangladesh, almost half of newborns had a birth weight of less than 2500 g,^{6,18} although recent country estimates indicate a change toward lower prevalence.¹⁷ Typically, Bangladeshi women are slender and short and have a low weight gain in pregnancy.¹⁹ Anemia and iron deficiency are also prevalent,²⁰ as well as zinc deficiency, vitamin B₁₂ deficiency,²¹ and vitamin A deficiency.²²

The high level of undernutrition among women and children in Bangladesh prompted the initiation of general nutrition intervention programs (Bangladesh Integrated Nutrition Project, later National Nutrition Program) that included food supplementation. Benefitting from an excellent research infrastructure in Matlab, Bangladesh, we studied the effects of different timing of food supplementation combined with multiple micronutrients on maternal hemoglobin level, birth weight, and child survival up to the age of 5 years. We hypothesized that prenatal mul-

tiples micronutrient supplementation (MMS), as well as an early invitation to a daily food supplementation, would increase maternal hemoglobin level at 30 weeks' gestation, birth weight, and infant survival, and that a combination of these interventions (early invitation with MMS) would further improve these outcomes in comparison with usual invitation to food supplementation and supplementation with 60 mg of iron and 400 µg of folic acid.

METHODS

Trial Location and Population

This trial was conducted in Matlab subdistrict, rural Bangladesh, where the population receives health services from the International Center for Diarrheal Disease Research, Bangladesh (ICDDR,B). The Health and Demographic Surveillance System has been in place since mid-1960s, covering a population of about 220 000 people in more than 140 villages with monthly updates of demographic and selected health information. Women were enrolled in the study after giving their written informed consent. Enrolled women were told that they could withdraw from the study at any point without affecting their access to and use of routine health services. Confidentiality of information was strictly followed. The ethical review committee at ICDDR,B and the research ethics committee at Uppsala University, Uppsala, Sweden, approved the study.

If a woman reported to the community health research worker of ICDDR,B (who visits her every month) that her last menstrual period (LMP) was overdue or that she was pregnant, she was offered a pregnancy test (ACON, San Diego, California) and the date of her LMP was recorded. The LMP date was used for the calculation of gestational age. A woman who tested positive was encouraged to visit the ICDDR,B clinic as soon as possible, preferably at 8 to 10 weeks of pregnancy, where an ultrasound examination was offered. The following eligibility criteria had to be met for enrollment: viable fetus, gestational age of less than 14 weeks by ultrasound examina-

tion, no severe illness, and written consent for participation.

Design and Interventions

A randomized factorial experiment with 2 food groups and 3 micronutrient groups resulted in a total of 6 groups (FIGURE). The 2 food supplement groups were invited to start supplementation (1) immediately after detection of pregnancy (early invitation assignment) or (2) at the time of their choosing (usual care invitation in this community). Three types of micronutrient supplements were capsules containing 30 mg of iron (fumarate) and 400 µg of folic acid, 60 mg of iron and 400 µg of folic acid, or MMS containing 15 recommended micronutrients²³ (30 mg of iron [fumarate], 400 µg of folic acid, 800 µg of RE vitamin A [retinyl acetate], 200 IU of vitamin D [D3], 10 mg of vitamin E [α -tocopherol acetate], 70 mg of vitamin C, 1.4 mg of vitamin B₁ [thiamine mononitrate], 1.4 mg of vitamin B₂ [riboflavin], 18 mg of niacin, 1.9 mg of vitamin B₆ [pyridoxine hydrochloride], 2.6 µg of vitamin B₁₂ [cyanocobalamin], 15 mg of zinc [sulfate], 2 mg of copper [sulfate], 65 µg of selenium [sodium selenite], and 150 µg of iodine [potassium iodide]).

The usual care invitation with daily dose of 60 mg of iron and 400 µg of folic acid was included as part of the standard program. The rationale for providing the treatment with 30 mg of iron and 400 µg of folic acid was primarily related to the maternal hemoglobin level outcome, but also to offer an iron-folate alternative with the same amount of iron as in the MMS group. All groups received a micronutrient supplement.

The ongoing, government-supported national program in Matlab provided an energy-protein supplement to all pregnant women. The supplement was provided in plastic packets to be mixed with water and contained 80 g of roasted rice powder, 40 g of roasted pulse powder, 20 g of molasses, and 12 mL (6 g) of soybean oil, which provided 608 kcal of energy and 18 g of vegetable protein. Community nutri-

tion centers provided the supplements for 6 days per week. Pregnant women were individually randomized to be invited to the feeding program either immediately after ascertainment of pregnancy (early assignment at around 9 weeks of pregnancy based on reported LMP) or to enroll at the time of their choosing (usually from around 20 weeks of pregnancy).

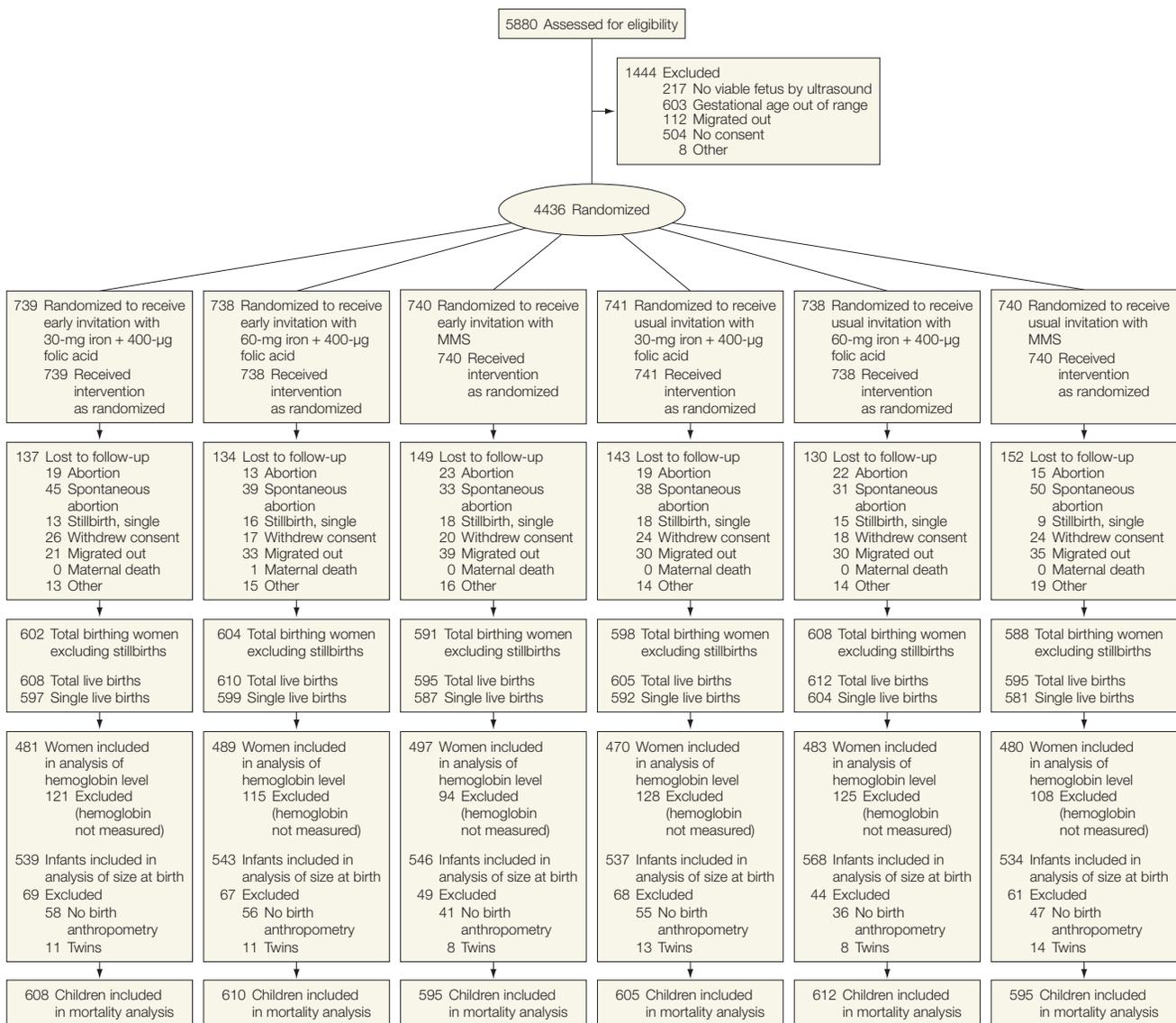
Women randomized to early assignment were encouraged to attend nutrition centers and their names were given to the nutrition program. In addition, all pregnant women were individually randomized to receive 1 of the 3 types of micronutrient supplements daily. The micronutrient supplements were offered to the enrolled pregnant women at the 14 weeks' clinic visit. The 3 types

of micronutrient capsules looked identical and were distributed in special bottles (eDEM, Aprex). Each bottle contained 35 capsules and was replaced at each monthly home visit by interviewers.

Outcomes

The primary outcomes were maternal hemoglobin level at 30 weeks' gesta-

Figure. Study Flow of Women and Infants



MMS indicates multiple micronutrient supplementation (15 micronutrients, including 30-mg iron and 400-µg folic acid). Pregnancy outcomes were registered as spontaneous abortion (unintended loss of a fetus within 28 weeks' gestation as determined by reported last menstrual period), induced abortion (intentional loss of a fetus within 28 weeks' gestation), stillbirth (birth of a dead fetus after 28 weeks' gestation), or live birth (birth of a fetus with any sign of viability). Fetal loss was defined as spontaneous abortions plus stillbirths, excluding induced abortions.

tion, birth weight, and infant mortality. Secondary outcomes reported herein were birth length and head circumference, gestational age at birth, and perinatal and child mortality. Secondary outcomes, which have been or will be reported elsewhere, included psychomotor development in infancy,²⁴ effect on micronutrient status in infancy,²⁵ and morbidity, immune function, childhood growth, body composition, and metabolic markers at 4.5 years.

Follow-up and Outcome Assessments

The participating pregnant women returned to the clinics on 3 more occasions (14, 19, and 30 weeks' gestation) and were followed up monthly at home by study interviewers. Pregnancy outcomes were registered (spontaneous abortion, induced abortion, stillbirth, live birth). Spontaneous abortion was defined as unintended loss of a fetus within 28 weeks of gestation as determined by reported LMP. Induced abortion was defined as intentional loss of a fetus within 28 weeks of gestation. Stillbirth was defined as birth of a dead fetus after 28 weeks of gestation. Fetal loss was defined as spontaneous abortions plus stillbirths excluding induced abortions. Live birth was defined as birth of a fetus with any sign of viability. Infant death was defined as death of a live birth before 12 months, and under 5-year mortality as death of a live birth before 5 years old. Out-migration was also registered during the visits to the participants' households. The study clinics provided antenatal health services at the clinic visits as well as in-between if needed. The community health research worker registered the date of LMP at enrollment. If LMP date was missing, the date was imputed from the estimated gestational age by ultrasound at the first clinic visit. Date of delivery was registered and used to calculate gestational age at birth.

At monthly home visits, the interviewers asked a series of questions to assess adherence with food supplementa-

tion during the previous 30 days. An eDEM device in the micronutrient bottle cap that was equipped with a counting device and a small microprocessor monitored adherence to the micronutrient supplementation. Time and date were recorded each time the capsule-bottle was opened. The information in the caps was downloaded into a computer from bottles collected from the enrolled women.

Information on specified gastrointestinal adverse effects was collected after 4 weeks of micronutrient supplementation. Hemoglobin level was assessed on venous blood by HemoCue (HemoCue AB) at clinic visits at 14 and 30 weeks' gestation. Anemia was defined as a hemoglobin level of less than 110 g/L. The assessment of hemoglobin was delayed at start of trial, contributing to most of the missing information on that outcome (hemoglobin data were missing for 691 of 2900 attending the 30-week clinic visit).

The attending nurse performed anthropometry when deliveries took place at health facilities. The Maternal and Infant Nutrition Interventions in Matlab (MINIMat) study had established a birth notification system for those women who delivered at home. Trained paramedics measured the birth anthropometry mostly within 72 hours of birth. However, measurements were made even if the newborns were reached after 72 hours. All birth weights were measured by SECA electronic scales (SECA GmbH), which were precise to 10 g. Locally manufactured, collapsible length boards, which were precise to 1 mm, were used to measure the recumbent length of the newborn using standard procedures. Head circumference was measured with a nonstretch tape to the nearest 0.1 cm. Refresher training of the interviewers on methods to collect data and anthropometric measurements was conducted periodically and reliability data for anthropometric measurements were collected on these occasions. Weighing equipment was calibrated daily with standard weights. An independent team of data collectors repeated about a 5%

random sample of the interviews and measurements and data from the 2 interviews were subsequently compared.

Ascertaining and attributing causes of death were performed in accordance with the verbal autopsy standards that have been developed by the International Network for Demographic Evaluation of Populations and Their Health network and the World Health Organization.²⁶ Community health research workers detected and recorded death through monthly household visits. Information was collected through home interviews with caretakers or relatives who had lived with the deceased in the same household at the time of death. Three independent physicians reviewed the available information and assigned the codes of the *International Statistical Classification of Diseases, 10th Revision*. In case of disagreement, the cause of death was finally assigned after a consensus process.

Sample Size and Randomization

The sample size was estimated using birth weight as the primary outcome variable with 70 g determined to be the minimum important difference among the groups. Assuming an SD of 400 g, the estimated sample size with 90% power and type I error of .05 was 686 women in each group (ie, 4116 in the 6 groups). Adjusting for 5% refusal, 11% loss during pregnancy and 9% loss due to out-migration, the total sample size required was 5300 women. The observed average group size of 545 live births with birth weight measurement allowed for 82% power for a 70-g difference between any 2 groups and demonstrating reduction in infant mortality by 1 of the combined treatments of relative risk (RR) of 0.5 (95% CI, 0.27-0.99).

A computer-generated register was used for randomization, which included study identity numbers with random assignment of food groups (early or usual invitations) and micronutrient groups. Each micronutrient group had been given 4 different number codes to decrease the risk of un-

blinding, with randomization performed in blocks of 12, and independently for each of 4 ICDDR,B clinics. The micronutrient supplementation was thus double-blinded and the food supplementation was randomly allocated but not blinded. Randomization codes were safely kept at the administrative office of ICDDR,B and were not broken until after performing the intention-to-treat analyses.

Analysis

Baseline characteristics of all randomized women were compared among the 6 treatment groups. Characteristics of randomized women dropping out from the trial were also compared among the treatment groups. Adherence with the randomized treatments was analyzed based on the reported number of food packages received from start of the food supplementation to the week 30 examination, and number of micronutrient bottle openings (recorded by the eDEM device) from enrollment to week 30 examination.

Anthropometric measurements performed during the first 24 hours were used without adjustments. Measurements taken from 24 hours up to 30 days after birth were adjusted using an SD score transformation assuming that infants tend to remain in the same relative position in the anthropometric distribution during this period.¹⁸ Analysis of newborn anthropometric data was by intention-to-treat. Analysis of variance was used to test for main effects of food and micronutrient groups and for any difference among the 6 groups. A *t* test was used to compare early invitation and MMS with the standard program. $P < .05$ (1-sided, based on a hypothesis formulated a priori) was considered statistically significant.

Analyses of hemoglobin levels at 30 weeks' gestation were by intention-to-treat using analysis of variance, adjusting for significant baseline (14 weeks' gestation) differences. Analysis of fetal loss and mortality of live births before 5 years was by intention-to-treat. Number of spontaneous abortions, stillbirths, and infant deaths was analyzed

per treatment group. Stillbirth rates per 1000 births, neonatal mortality rates per 1000 live births, perinatal mortality rates per 1000 live births were calculated, as well as RRs for fetal loss and perinatal mortality with 95% CIs. The RR for infant and under 5-year mortality was calculated as hazards ratios (HRs) with 95% CIs based on Cox proportional hazards regression model analysis (controlling that proportional hazards are constant over time) using exact time (age in days) for any losses to follow-up as well as mortality outcomes before 365 days and 1825 days of age, respectively, and with the standard program as the reference group. All analyses were conducted with PASW statistics version 18.0 (IBM Corporation).

RESULTS

Between November 11, 2001, and October 30, 2003, 4436 pregnant women were enrolled and randomized to the 6 food and micronutrient treatments. We completed the follow-up of children younger than 5 years on June 23, 2009 (Figure). There were 845 of 4436 losses to follow-up (19%) before birth; the main reasons were fetal loss (10%), out-migration from the study area (4%), or refusal to participate (3%), especially during Ramadan in November 2002 and in October 2003. There were 3625 live births. Data on birth anthropometry were available for analysis for 3267 singleton newborns. Numbers of women lost to follow-up did not differ among the treatment groups. Baseline characteristics of women with incomplete information did not differ across supplementation groups, except that maternal age was 1.4 years older in the early invitation with 60 mg of iron and 400 µg of folic acid vs the standard program ($P = .03$).

Participating women were recruited at 9.5 (SD, 2.2) weeks' gestation (TABLE 1). They had an average weight of 45 kg and a height of 150 cm. One-third of the women were primiparous, one-third were illiterate, and one-

fifth experienced occasional or constant deficit in their perceived income-expenditure status. The characteristics of the women and their households at baseline were comparable across treatment groups. Forty percent of the mothers had skilled assistance at delivery (no difference among treatment groups, $P = .75$).

By design, those women allocated to the early invitation to food supplementation consumed more packages of supplements than those allocated to the usual timing of invitation (mean difference, 30 packages from enrollment to week 30 examination) (eTable 1, <http://www.jama.com>). The early invitation group reportedly consumed fewer packages than theoretically could be expected for the measurement period (from approximately 9 to 30 weeks' gestation), and the usual care invitation group consumed the expected number of packages (from approximately 20 to 30 weeks' gestation). The early invitation with MMS group reported consuming a mean of 6 more packages than the early invitation with 30 mg of iron and 400 µg of folic acid and the early invitation with 60 mg of iron and 400 µg of folic acid groups, but there was no significant interaction for food × micronutrient groups ($P = .06$). On average, the participants took 77 micronutrient capsules from week 14 to week 30. The MMS groups took fewer capsules than the other groups ($P = .03$) and the early invitation group also took fewer micronutrient capsules on average ($P = .02$). There was no interaction for food × micronutrient groups in mean micronutrient intake ($P = .69$).

Constipation was the most common adverse reaction (30%), followed by nausea (18%) and heartburn (10%) (eTable 2). There was no difference in reported frequency of these common adverse effects. Although less common but a more severe adverse effect, vomiting occurred to a larger extent in the MMS group (11.6%) than in the 60 mg of iron and 400 µg of folic acid group (6.9%, $P = .002$) and the 30 mg of iron and 400 µg of folic acid group (7.1%, $P = .003$).

Maternal Hemoglobin Level

No interaction was found between food and micronutrient supplementation groups on hemoglobin levels at 30 weeks' gestation ($P = .84$). The adjusted mean hemoglobin level concentration at 30 weeks' gestation was 115.0 g/L (95% CI, 114.4-115.5 g/L), with no significant difference among micronutrient groups (TABLE 2). Women in the early invitation group had a small (0.9 g/L; 95% CI, 0.1-1.7 g/L) but statistically significant ($P = .03$) lower hemoglobin level concentration than those in the usual invitation group. The proportion of women with anemia at 30 weeks' gestation was 32.9%, without any differences among the treatment groups ($P = .57$).

Anthropometry and Gestational Age at Birth

The mean (SD) birth weight was 2694 (411) g (95% CI, 2680-2708 g) (2648

[392] g for girls and 2738 [424] g for boys). Overall, 31% of newborns weighed less than 2500 g. There was no significant difference in birth weight among treatment groups ($P = .35$) (TABLE 3), and no main-effect differences between food groups ($P = .27$) or among micronutrient groups ($P = .52$) existed. Mean (SD) length of newborns was 47.4 (2.2) cm and gestational age at birth was 39.1 (2.3) weeks, without any difference among treatment groups ($P = .26$ and $P = .18$, respectively).

Mortality

No significant difference was found in infant mortality risks when comparing early vs usual invitation to food supplementation in pregnancy (early invitation: HR, 0.82; 95% CI, 0.58-1.15). Similarly, infant mortality risks did not significantly differ among mi-

cronutrient treatment groups (60 mg of iron and 400 μ g of folic acid: HR, 1.0 [reference]; 30 mg of iron and 400 μ g of folic acid: HR, 0.82; 95% CI, 0.55-1.22; and MMS: HR, 0.70; 95% CI, 0.46-1.06).

Infant mortality rate and under 5-year mortality were lower among women randomized to early invitation to food supplementation with MMS (16.8 and 18.0 per 1000 live births, respectively) compared with the standard program (44.1 and 54.0 per 1000 live births, respectively) (TABLE 4). The corresponding HR for infant mortality was 0.38 (95% CI, 0.18-0.78). The HR for neonatal mortality and for under 5-year mortality also showed significantly lower mortality for early invitation with MMS compared with the standard program (Table 4). Usual care invitation with MMS had the highest infant mortality rate (47.1 per 1000 live births).

Table 1. Baseline Participant and Household Characteristics

Characteristics	Early Invitation to Food Supplementation			Usual Invitation to Food Supplementation		
	30-mg Iron + 400- μ g Folic Acid (n = 739)	60-mg Iron + 400- μ g Folic Acid (n = 738)	Multiple Micronutrients (n = 740) ^a	30-mg Iron + 400- μ g Folic Acid (n = 741)	60-mg Iron + 400- μ g Folic Acid (n = 738)	Multiple Micronutrients (n = 740) ^a
	Mean (SD)					
Age, y	26.1 (5.8)	26.5 (6.1)	26.6 (6.3)	26.4 (6.0)	26.0 (5.8)	26.1 (5.8)
Gestational age at enrollment, wk	9.4 (2.2)	9.4 (2.0)	9.5 (2.2)	9.3 (2.2)	9.4 (2.3)	9.5 (2.2)
Weight at enrollment, kg	45.3 (7.0)	45.4 (6.6)	45.4 (6.8)	45.3 (7.3)	45.3 (6.6)	45.5 (7.0)
Height, cm	149.5 (5.6)	149.9 (5.2)	149.9 (5.2)	149.8 (5.3)	149.9 (5.0)	149.6 (5.6)
Enrollment BMI	20.0 (2.7)	20.2 (2.7)	20.2 (2.8)	20.1 (2.7)	20.2 (2.6)	20.3 (2.6)
Hemoglobin level at 14 wk gestation, g/L	116 (13)	116 (13)	117 (13)	116 (12)	116 (13)	118 (13)
	No. (%)					
Parity						
0	174 (32)	178 (33)	159 (31)	166 (31)	173 (30)	179 (33)
1	153 (28)	148 (27)	161 (28)	150 (28)	163 (29)	155 (29)
≥ 2	212 (39)	217 (40)	226 (41)	221 (41)	232 (41)	200 (38)
Mother's schooling, y						
0	176 (33)	160 (30)	183 (34)	168 (31)	175 (31)	161 (30)
1-4	70 (13)	61 (11)	67 (12)	61 (11)	59 (10)	60 (11)
≥ 5	293 (54)	322 (59)	296 (54)	308 (57)	334 (59)	313 (59)
Father's schooling, y						
0	167 (31)	154 (28)	172 (32)	157 (29)	173 (30)	152 (29)
1-4	73 (14)	48 (9)	72 (13)	58 (11)	66 (12)	56 (10)
≥ 5	297 (55)	340 (63)	297 (55)	320 (60)	328 (58)	323 (61)
Perceived income-expenditure status						
Surplus	158 (29)	147 (27)	165 (30)	126 (24)	150 (27)	138 (26)
Breakeven	276 (51)	304 (56)	275 (50)	295 (55)	303 (53)	292 (55)
Occasional deficit	90 (17)	77 (14)	81 (15)	100 (19)	100 (18)	89 (17)
Constant deficit	14 (2.6)	15 (2.8)	25 (4.8)	16 (3.0)	14 (2.5)	15 (2.8)

Abbreviation: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared.

^aMultiple micronutrients include 15 micronutrients, including 30-mg iron and 400- μ g folic acid.

The rate of spontaneous abortions was not significantly different between early invitation with MMS and the standard program (Table 4). However, usual care invitation with MMS had a significantly higher occurrence of spontaneous abortions than the standard program did (RR, 1.59; 95% CI, 1.02-2.47). The RR of fetal loss including spontaneous abortions and stillbirths did not significantly differ across groups.

The main causes of infant mortality were asphyxia (intrapartum-related neonatal deaths), infections, and conditions associated with preterm birth or intrauterine growth restriction (eTable 3). The number of neonatal deaths from asphyxia was highest in the usual invitation with MMS group (14 per 595 live births), which was 7 times higher than the early invitation with MMS group (2 per 595 live births, $P=.004$)

and double that of the standard program (7 per 612 live births, $P=.13$).

COMMENT

Although the 2 treatment groups affected maternal hemoglobin level only marginally and did not affect birth weight, pregnant women who received multiple micronutrients combined with an early invitation to food supplementation substantially improved survival of their offspring.

Previous nutritional interventions in pregnancy have mainly consisted of either balanced protein-energy supplementation or single or multiple micronutrient interventions.⁴ Our trial is unique in combining the timing of food supplementation with different micronutrient alternatives based on the understanding that food and micronutrient deficiencies usually coexist and that obtaining a satisfactory dietary in-

take in early pregnancy may be crucial for placenta function and fetal development.

A meta-analysis including 12 trials performed by the Maternal Micronutrient Supplementation Study Group demonstrated a small increase in birth weight (22.4 g; 95% CI, 8.3-36.4 g) and a 10% reduction in the occurrence of low birth weight by MMS, but no significant effects on birth length or gestational age at birth in comparison with iron-folic acid supplementation alone.^{8,9} The most recent meta-analysis, including a few more trials, showed 9% reduction in the occurrence of small-for-gestational-age outcome (RR, 0.91; 95% CI, 0.86-0.96).¹⁰

In our trial, mean maternal hemoglobin level was lower in the early invitation to food supplementation vs the usual invitation group (114.5 vs 115.4 g/L). In addition, in agreement with

Table 2. Maternal Hemoglobin Level at 14 and 30 Weeks' Gestation by Supplementation Groups^a

	Mean (95% CI)						P Value ^b
	Maternal Micronutrient Supplementation			Maternal Food Supplementation			
	60-mg Iron + 400- μ g Folic Acid (n = 972)	Multiple Micronutrients (n = 977)	30-mg Iron + 400- μ g Folic Acid (n = 951)	Usual Invitation (n = 1433)	Early Invitation (n = 1467)		
Hemoglobin level at 14 wk gestation, g/L	115.9 (115.2 to 116.7)	117.3 (116.5 to 118.1)	116.5 (115.7 to 117.4)	116.7 (116.1 to 117.4)	116.5 (115.8 to 117.1)		.58
Difference	1 [Reference]	1.3 (0.2 to 2.5) ^c	0.6 (-0.5 to 1.7)	1 [Reference]	0.3 (-1.2 to 0.7)		
Hemoglobin level at 30 wk gestation, g/L	114.9 (114.1 to 115.7)	114.9 (114.2 to 115.7)	115.0 (114.3 to 115.8)	115.4 (114.8 to 116.1)	114.5 (113.8 to 115.1)		.03
Difference, adjusted ^d	1 [Reference]	-0.4 (-1.5 to 0.6)	-0.1 (-1.1 to 1.0)	1 [Reference]	-0.9 (-1.7 to -0.1) ^e		

^aMultiple micronutrients include 15 micronutrients, including 30-mg iron and 400- μ g folic acid.

^bGeneral linear regression, P values for main effect micronutrient supplementation and main effect food supplementation, respectively, unadjusted models, interaction food \times micronutrient supplement group (for hemoglobin level at 14 weeks' gestation, $P=.76$; and for hemoglobin level at 30 weeks' gestation, $P=.84$).

^cSignificantly ($P=.02$) different than 60 mg of iron and 400 μ g of folic acid group.

^dGeneral linear regression, models adjusted for hemoglobin level at 14 weeks' gestation.

^eSignificantly ($P=.04$) different from usual invitation to food supplementation group.

Table 3. Infant Anthropometric Outcomes by Food Supplementation Groups^a

	Mean (95% CI)						P Value
	Early Invitation to Food Supplementation			Usual Invitation to Food Supplementation			
	30-mg Iron + 400- μ g Folic Acid (n = 539)	60-mg Iron + 400- μ g Folic Acid (n = 543)	Multiple Micronutrients (n = 546)	30-mg Iron + 400- μ g Folic Acid (n = 537)	60-mg Iron + 400- μ g Folic Acid (n = 568)	Multiple Micronutrients (n = 534)	
Birth weight, g	2689 (2653-2725)	2717 (2685-2749)	2696 (2663-2729)	2688 (2651-2725)	2665 (2631-2699)	2710 (2675-2745)	.35
Gestational age at birth, wk	38.8 (38.6-39.0)	38.9 (38.7-39.1)	38.9 (38.7-39.1)	38.8 (38.6-39.0)	38.8 (38.6-39.0)	39.1 (38.9-39.3)	.18
Birth length, cm	47.6 (47.4-47.8)	47.9 (47.7-48.1)	47.7 (47.5-47.9)	47.6 (47.4-47.8)	47.7 (47.5-47.9)	47.7 (47.5-47.9)	.26
Head circumference, cm	39.1 (39.0-39.2)	39.2 (39.1-39.3)	39.1 (39.0-39.2)	39.1 (38.9-39.3)	39.1 (39.0-39.2)	39.3 (39.2-39.4)	.18

^aMultiple micronutrients include 15 micronutrients, including 30-mg iron and 400- μ g folic acid. P values were assessed by F test comparing the means among the 6 food and micronutrient groups.

other studies,^{10,12} we did not find any difference between MMS and 60 mg of iron and 400 µg of folic acid on hemoglobin level outcome. Despite multiple micronutrient deficiencies in the study population,²¹ the lack of difference between MMS and 30 mg of iron indicates that the additional micronutrients provided by MMS did not have any additional effect on hemoglobin level at 30 weeks' gestation. Furthermore, the 60 mg of iron and 400 µg of folic acid treatment with its double amount of iron compared with 30 mg of iron (same amount of folic acid) did not produce any different hemoglobin level concentration at 30 weeks' gestation. Although this may in part be due to low prevalence of iron deficiency at 14 weeks' gestation,²¹ it is also likely that maximum hemoglobin level response

also was obtained by the lower amount of iron provided in MMS and 30 mg of iron. A dose-response association has previously been shown between ingested iron supplements and hemoglobin level concentration that exhibits a plateau at approximately 1800 mg ingested iron in Tanzania²⁷ and approximately 2400 mg in Bangladesh.²⁸ The average amount of iron ingested in this trial (4620 mg in the 60 mg of iron group, 2310 mg in the 30 mg of iron group, and 2190 mg in the MMS group) may all have been sufficient to produce maximum response.

Confirming our hypothesis, we showed that children of mothers assigned to MMS combined with an early invitation to food supplementation had reduced under 5-year mortality in comparison with the standard program. The

early invitation with MMS group had few deaths caused by asphyxia or infections. The frequency of skilled attendance at delivery was the same across treatment groups (40%), which should preclude any differential perinatal care provided by the health care services as an explanation to our findings.

The effect of timing of prenatal food supplementation on survival of the offspring has not been studied before in human trials. Furthermore, no previous studies have analyzed the effect on survival by timing of prenatal food supplementation combined with a randomization to MMS or iron-folate supplementations. The latest meta-analysis of balanced prenatal protein-energy supplementation trials showed a significant reduction in risk of still-

Table 4. Fetal Loss and Infant Mortality Outcomes by Food Supplementation Groups^a

	Early Invitation to Food Supplementation			Usual Invitation to Food Supplementation		
	30-mg Iron + 400-µg Folic Acid	60-mg Iron + 400-µg Folic Acid	Multiple Micronutrients	30-mg Iron + 400-µg Folic Acid	60-mg Iron + 400-µg Folic Acid	Multiple Micronutrients
	No. of Women or Infants					
Pregnant women randomized	739	738	740	741	738	740
Abortions	19	13	23	19	22	15
Spontaneous abortions	45	39	33	38	31	50
Stillbirth single	13	16	18	18	15	9
Stillbirth twin	0	1	1	0	0	0
Birthing women excluding stillbirths	602	604	591	598	608	588
Live single births	597	599	587	592	604	581
Total live births including twins	608	610	595	605	612	595
Early neonatal deaths, aged 0-6 d	15	18	4	15	18	21
Late neonatal deaths, aged 7-27 d	2	2	3	0	5	4
Postneonatal deaths, aged 28-364 d	9	6	3	4	4	3
Child deaths, aged 365-1824 d	6	4	1	2	6	6
	Rate per 1000 Births					
Stillbirth rate	20.9	27.1	30.9	28.9	23.9	14.9
Mortality rate						
Neonatal	28.0	32.8	11.8	24.8	37.6	42.0
Perinatal	45.5	56.4	37.7	53.6	53.0	50.3
Infant	42.8	42.6	16.8	31.4	44.1	47.1
	Relative Risk (95% CI)					
Fetal loss ^b	1.3 (0.85-1.8)	1.2 (0.82-1.8)	1.1 (0.76-1.7)	1.2 (0.82-1.8)	1 [Reference]	1.3 (0.86-1.9)
Perinatal mortality ^c	0.86 (0.52-1.4)	1.1 (0.68-1.7)	0.71 (0.42-1.2)	1.0 (0.66-1.5)	1 [Reference]	0.95 (0.59-1.5)
	Hazard Ratio (95% CI)					
Neonatal mortality, within first 28 d	0.74 (0.40-1.4)	0.87 (0.48-1.6)	0.31 (0.13-0.72)	0.66 (0.34-1.3)	1 [Reference]	1.1 (0.64-2.0)
Infant mortality, aged 0-364 d	0.97 (0.63-1.8)	0.97 (0.56-1.7)	0.38 (0.18-0.78)	0.71 (0.39-1.3)	1 [Reference]	1.1 (0.63-1.8)
Under 5-year mortality	0.92 (0.57-1.5)	0.89 (0.57-1.5)	0.34 (0.18-0.65)	0.67 (0.69-1.7)	1 [Reference]	1.1 (0.69-1.7)

^aMultiple micronutrients include 15 micronutrients, including 30-mg iron and 400-µg folic acid. The usual invitation to food supplementation with 60-mg iron and 400-µg folic acid was selected as the reference, per usual program practice.

^bFetal wastage excluding induced abortions per 1000 pregnancies.

^cStillbirths plus early neonatal deaths per 1000 births.

birth. A tendency toward lower neonatal mortality across the included trials in diverse settings remained nonsignificant.²⁹ A meta-analysis of prenatal MMS did not find any reduction in stillbirth, perinatal mortality, or neonatal mortality.¹¹

Animal studies,³⁰ supported by epidemiological evidence from human famines,³¹ have shown that there are critical periods in the mother's dietary intake during pregnancy that can program metabolism and influence future health without altering the size at birth. The positive effect on survival in the MINIMat trial was evidently not mediated by changes in the fetal growth trajectory and size at birth. However, the combination of a balanced protein-energy supplement from approximately week 9 of gestation with MMS from week 14 implied a maternoplacental nutrient supply that favored healthy fetal development and infant survival, with the lowest incidence of asphyxia deaths and infectious disease mortality. In animal experiments, undernutrition in early gestation is associated with impaired responses of the hypothalamic-pituitary-adrenal axis.³⁰ Dietary deficiencies during early gestation may also affect other homeostatic mechanisms. Food supplementation in early gestation combined with MMS may therefore—even in humans—have the potential to promote adequate responses of the offspring to the stresses at birth and to the threats of perinatal infections.³²

Mortality rates for offspring were highest among the women randomized to MMS combined with the usual invitation to food supplementation, mainly caused by asphyxia. Furthermore, this treatment group had significantly higher incidence of spontaneous abortions. The late pregnancy losses were lower in the usual invitation with MMS group, resulting in no difference in RR of total fetal loss across treatment groups. Pooled data from 2 independent trials in Nepal suggested increased risks of perinatal and neonatal mortality when mothers had received

MMS vs iron-folate alone.³³ In the Burkina Faso trial³⁴ of prenatal MMS, the risk of perinatal death was marginally significantly increased in the MMS group (odds ratio [OR], 1.78; 95% CI, 0.95-3.32) and among primiparous women this effect was more pronounced (OR, 3.44; 95% CI, 1.10-10.70). Selecting the trials with a majority of births taking place at home in the recent meta-analysis,¹⁰ MMS was associated with an increased risk of neonatal mortality (RR, 1.47; 95% CI, 1.13-1.92). Given that less than half the pregnant women in South Asia or sub-Saharan Africa has a skilled attendance at delivery or benefit from an institutional delivery,¹⁷ the potential risk for neonatal death with blanket prenatal MMS is a concern. In the Sarlahi trial in Nepal,³⁵ symptoms of birth asphyxia increased by approximately 60% in infants of women who received MMS vs vitamin A alone. The reason for this is so far unknown, although the authors speculate whether larger newborns or an increased uterine sensitivity to oxytocin could explain the finding.³⁶

Pregnant women participating in the MINIMat trial may be considered typical for the poor, mainly rice-farming population in the Bangladesh delta. In comparison with the study populations in the other recent MMS trials, these women were relatively short (mean height, 149.8 cm) and, typical for many South Asian countries, a high proportion of their newborns had low birth weights (31% in this trial). Other studies have shown an estimated mean energy intake at 5 to 7 months' gestation of 1464 kcal/d.¹⁹ In such a population, the need for not only micronutrients but also a balanced protein-energy supplementation from early gestation may be evident. These indicators of low dietary intake and poor nutritional status limit the external validity of the findings in relationship to populations of pregnant women with better nutritional status.

Scientists and policymakers have recommended replacing the current iron-folic acid supplements with MMS in the

package of health and nutrition interventions delivered to pregnant women to improve size at birth and child growth and development.^{4,37} Other studies have questioned this view based on the limited size of the effect on birth weight and the absence of positive effect on fetal and neonatal survival.³⁶ The MINIMat trial provides evidence that mortality of the offspring was reduced if multiple micronutrients were combined with a balanced protein-energy supplementation that began early in pregnancy. The macronutrient deficiencies in the diet of pregnant women vary among populations. Scaling up prenatal MMS in areas where dietary intake in early pregnancy is suboptimal may create an increased risk of fetal loss and infant mortality.

Author Affiliations: Department of Women's and Children's Health, International Maternal and Child Health, Uppsala University, Uppsala, Sweden (Drs Persson and Ekström); International Center for Diarrheal Disease Research, Dhaka, Bangladesh (Drs Arifeen and Yunus); Division of Nutritional Sciences, Cornell University, Ithaca, New York (Dr Rasmussen); and Department of Health Promotion, Education, and Behavior, Arnold School of Public Health, University of South Carolina, Columbia (Dr Frongillo).

Author Contributions: Dr Persson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Persson, Arifeen, Ekström, Rasmussen, Frongillo, Yunus.

Acquisition of data: Persson, Arifeen, Ekström, Frongillo, Yunus.

Analysis and interpretation of data: Persson, Arifeen, Ekström, Rasmussen, Frongillo, Yunus.

Drafting of the manuscript: Persson, Arifeen, Rasmussen.

Critical revision of the manuscript for important intellectual content: Persson, Arifeen, Ekström, Frongillo, Yunus.

Statistical analysis: Persson, Arifeen, Frongillo.

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The MINIMat (Maternal and Infant Nutrition Interventions in Matlab) Study Team (in alphabetical order): International Center for Diarrheal Disease Research, Dhaka, Bangladesh (ICDDR,B): Dewan Alam, MBBS, PhD, Lauren S. Blum, PhD, Badal Dhar, MHI, Jena Hamadani, PhD, Waheedul Hoque, MBBS, Iqbal Kabir, MBBS, PhD, Ruchhira T. Naved, PhD, Anisur Rahman, MBBS, PhD, Mahfuzar Rahman, MBBS, PhD, Motiur Rahman, MBBS, PhD (currently at Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam), Rubhana Raqib, PhD, Kuntal K. Saha, MBBS, PhD, Ru-

bina Shaheen, MBBS, Peter K. Streatfield, PhD, Fahmida Tofail, MBBS, PhD, MA Wahed, MSc, BRAC, Dhaka, Bangladesh; Mushtaque Chowdhury, PhD; Medical Research Council International Nutrition Group, London School of Hygiene and Tropical Medicine, London, England, and Medical Research Council Keneba, the Gambia: Sophie Moore, BSc, PhD, Andrew Prentice, BSc, PhD; Institute of Child Health, London, England; Sally G. McGregor, MD, FRCP; University of California, Davis: Bo Lönnerdal, PhD; Micronutrient Initiative, Ottawa, Ontario, Canada, and National Institute of Public Health, Cuernavaca, Mexico: Lynnette M. Neufeld, PhD; Karolinska Institutet, Stockholm, Sweden: Marie Vahter, PhD; University of Tsukuba, Tsukuba, Japan: Yukiko Wagatsuma, MD, PhD.

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