Published in final edited form as:

Am J Epidemiol. 2017 August 01; 186(3): 318–325. doi:10.1093/aje/kwx094.

Effects of Prenatal Micronutrient Supplementation on Spontaneous Preterm Birth: A Double-Blind Randomized Controlled Trial in China

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Conflict of interest: none declared.

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Abstract

In this secondary analysis of data from a double-blind randomized controlled trial carried out in northern China, we aimed to assess the effect of prenatal supplementation with multiple micronutrients (MMN) or iron + folic acid (IFA), versus folic acid (FA) alone, on risk of spontaneous preterm birth (SPB) and the impact of supplementation timing on SPB. A total of 18,775 nulliparous pregnant women enrolled between 2006 and 2009 were randomly assigned to receive daily FA, IFA, or MMN from the period before 20 weeks' gestation to delivery. The incidences of SPB for women consuming FA, IFA, and MMN were 5.7%, 5.6% and 5.1%, respectively. Compared with women given FA, the relative risks of SPB for those using MMN and IFA were 0.99 (95% confidence interval: 0.85, 1.16) and 0.89 (95% confidence interval: 0.79, 1.05), respectively. SPB incidence in women who started consuming FA, IFA, and MMN before the 12th week of gestation (4.6%, 4.2%, and 3.9%, respectively) was significantly reduced compared with starting supplement use on or after the 12th gestational week (6.9%, 7.2%, and 6.4%, respectively). Starting use of FA, IFA, or MMN supplements before the 12th week of gestation produced a 41%–45% reduction in risk of SPB. Early prenatal enrollment and micronutrient use during the first trimester of pregnancy appeared to be of particular importance for prevention of SPB, regardless of supplement group.

Keywords

China; folic acid; iron + folic acid; pregnancy; prenatal vitamin supplements; randomized controlled trials; spontaneous preterm birth; women

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Micronutrients are vitamins and minerals that are needed by the body in very small quantities but are necessary for human health. In low- and middle-income countries, many women are deficient in micronutrients due to poor diets. Pregnant women are particularly vulnerable to micronutrient deficiencies because of the increased nutritional requirements for the growth of the fetus and placenta and the expansion of red blood cell mass. Evidence has suggested that deficiencies in multiple micronutrients (MMN), rather than single-nutrient deficiencies, are common (1). It is therefore expected that providing a full complement of micronutrients in prenatal supplements may optimize the functional and health benefits to the mother and infant (2). However, evidence about the effects of MMN on pregnancy outcomes among undernourished populations is far from conclusive. In

developing countries, prenatal supplementation is mainly restricted to folic acid (FA) alone or iron plus folic acid (IFA). In China, only FA is recommended for the prevention of neural tube defects. In 1999, the United Nations Children's Fund, the World Health Organization, and the United Nations University designed an MMN supplement for pregnant and lactating women (the United Nations Multiple Micronutrient Antenatal Preparation (UNIMMAP)) that contains the Recommended Dietary Allowance of 15 vitamins and minerals (3). Various randomized trials have subsequently been conducted to evaluate the benefits of MMN supplementation (4–6). A recent meta-analysis provided support for a significant benefit of MMN supplementation during pregnancy in reducing the incidence of small-for-gestational-age birth and low birth weight in comparison with IFA (4, 5).

Preterm birth, a major global health problem and one that is strongly associated with neonatal mortality, as well as short- and long-term morbidity, has attracted extensive attention worldwide in recent years. However, understanding of the causes of preterm birth and the potential benefit of preventive interventions is poor (7). Nutrition is believed to play a role in the pathogenesis of preterm birth. Many studies have suggested that use of FA-containing MMN supplements during pregnancy has a protective effect against preterm birth relative to no supplementation (8–13). Some researchers have suggested that MMN may specifically be related to early preterm birth (8–10), and the timing of use may also be important in these associations because multivitamin use during the periconceptional period appears to be crucial (8, 9, 12). Two observational studies have also shown a protective effect of multivitamins on risk of spontaneous preterm birth (SPB) but not medically complicated preterm birth (9, 10). We recently reported that daily intake of 0.4 mg of FA alone, as compared with no intake during the periconceptional period, was associated with a reduced risk of SPB in a large population-based cohort study in China (14).

Between 2006 and 2009, we conducted a double-blinded, individual randomized controlled trial (clinicaltrials.gov identifier: NCT00133744) in rural areas of northern China to evaluate whether prenatal supplementation with MMN or IFA versus FA could reduce perinatal mortality (the primary outcome) and improve other secondary pregnancy outcomes (6). In the primary analysis of the trial results, we did not find a significant effect of MMN or IFA versus FA on live preterm births occurring at 28 weeks' gestation or later (6). In this post hoc secondary analysis, we examined whether MMN or IFA provided additional protective effects on risk of SPB relative to FA alone. We also aimed to determine whether the incidence of preterm birth varied by the timing of supplementation (<12 gestational weeks vs. ≥12 gestational weeks) for each of the 3 supplement groups.

METHODS

Study design and location

The study was designed as a double-blinded randomized controlled trial with 3 study groups (MMN or IFA vs. FA) in 5 counties in Hebei Province, northern China. The study protocol was approved by the institutional review boards of the US Centers for Disease Control and Prevention (Atlanta, Georgia) and Peking University (Beijing, China). All of the project counties are within 2–3 hours' drive of Beijing. The population of the study area is homogeneous and not very mobile. Basic health services are provided through 3-tier

(county, township, and village) health-care networks. Health facilities and service capacity are similar in the 5 counties.

Recruitment and menstrual monitoring

Before and during enrollment, extensive communication about the study occurred through television commercials, posters, and pamphlets. Women were told about the study during routine group counseling with township physicians. If women were willing to participate, they were given a custom-designed calendar to record the dates of their menstrual periods. Township or village health workers contacted women at least once a month by home visit or telephone call to record their dates of menstruation. Women were advised to undergo a pregnancy test in a hospital or village clinic 1–2 weeks after a missed menstrual period or if they believed they were pregnant. If pregnancy was confirmed, women were invited to enroll in the randomized controlled trial before 20 weeks of gestation.

Enrollment and intervention

Determination of eligibility and recruitment occurred at the prenatal examination at the county or township hospital. Women met the following inclusion criteria at enrollment: 1) resided in and received prenatal care in one of the 5 study counties; 2) recorded their dates of menstruation for 2 or more months before they became pregnant; 3) were at least 20 years of age; 4) were not more than 20 gestational weeks pregnant; 5) were nulliparous; 6) were legally competent; 7) had not consumed micronutrient supplements other than FA in the prior 6 months; 8) had a hemoglobin level greater than 10.0 g/dL; and 9) consented to participate. Eligible pregnant women were enrolled from May 2006 through April 2009 and were individually randomized at a 1:1:1 ratio to receive one of 3 types of daily supplements, as follows: FA (0.4 mg); IFA, consisting of FA (0.4 mg) plus iron (30 mg); and MMN (the UNIMMAP supplement contains the same amounts of iron and FA as the IFA supplement). All pills dispensed had same size, shape, and color regardless of content or lot number.

Follow-up and data collection

Women were followed from study enrollment (before 20 weeks' gestation) to their 4- to 8-week postpartum visit. Pregnant women were advised to make prenatal visits at least once during the first trimester, monthly during the second trimester, every other week from 28 weeks of gestation to 36 weeks of gestation, and weekly after 36 weeks' gestation. Each month, they were also asked to bring their pill bottles from the previous month to the clinic. At the examination, health-care workers counted the number of pills remaining, from which they calculated the number of pills taken and issued new pills for the next month. Physicians completed relevant measurements and collected data based on the field operation manual. Hemoglobin, birth weight, maternal weight, and infant weight were measured using standard equipment and methods (6). All study data were collected and entered into an electronic reproductive health surveillance system by the township physician at the time of the visit.

Definition of preterm birth

Gestational age at birth was measured as the number of days of completed gestation based on the date of delivery and the first day of the last menstrual period, obtained through

menstrual monitoring. Preterm birth was defined as a gestational age of 20–36 weeks. SPB was defined as preterm birth not associated with medical or obstetrical complications constituting indications for preterm delivery. Those indications included major external birth defects, stillbirth, termination of pregnancy, pregnancy-induced hypertension, chronic hypertension, diabetes, placenta previa, and placental abruption—similar to the indications defined by Bukowski et al. (10) and Li et al. (14). Early SPB was defined as SPB occurring between 20 and 31 completed weeks of gestation and late SPB as occurring between 32 and 36 completed weeks of gestation.

Statistical analysis

The baseline characteristics of participants, including women's age, height, body mass index (weight (kg)/height $(m)^2$) at enrollment, ethnicity, education, occupation, and gestational week at enrollment, were compared across treatment groups to assess the effectiveness of randomization. Compliance was defined as the number of supplements consumed divided by the number of days on which supplements were expected to be consumed (i.e., days between the dates of enrollment and delivery). The effects of the intervention were analyzed on the basis of an intent-to-treat principle. All participants with a known outcome were included in the analyses, irrespective of compliance. We calculated the incidence of SPB and subtypes (early SPB vs. late SPB) for each supplement group. Since the women's basic demographic characteristics were well-balanced across supplement groups, univariate logistic regression was used to estimate risk ratios for preterm birth by supplement group. All data were analyzed using SPSS software (version 20; SPSS Inc., Chicago, Illinois).

RESULTS

Figure 1 details the process of enrollment, randomization, and follow-up of the participants and participant selection for the current analysis. Among the 18,963 pregnant women considered for enrollment, 120 refused to participate in the study, and 68 were not eligible. A total of 18,775 women were randomly assigned to a study group. During the follow-up period, 61 women were lost to follow-up, 2 died, and 714 had spontaneous or induced abortions before the 20th week of gestation, leaving 17,998 women with known pregnancy outcomes. For the current analysis, we further excluded 67 women with twin or triplet pregnancies and 213 women who had medical or obstetrical complications constituting indications for preterm delivery. After these exclusions, a total of 17,718 women were included in the final analysis: 5,888 in the FA group, 5,920 in the IFA group, and 5,910 in the MMN group.

Table 1 shows baseline characteristics of the study population. Overall, the participants were predominantly young women (mean age = 23 years) with less than a high school education. Almost all participants (99%) were of Han ethnicity, and more than 90% of the women were farmers. The mean gestational age at recruitment was 12.1 weeks for all 3 groups. All baseline characteristics were well-balanced across the 3 intervention groups. The median level of compliance was 97% in all 3 study groups. Of the 17,718 pregnancies analyzed, 971 SPB infants were delivered, and the overall incidence of SPB was 5.5%.

Table 2 shows the risk of SPB according to maternal use of micronutrient supplements. The incidence of SPB was 5.7% for the FA group, 5.6% for the IFA group, and 5.1% for the MMN group. Relative to prenatal supplementation with FA alone, use of MMN or IFA did not have a significant effect on SPB risk, nor was there any effect for early or late SPB.

In order to examine the joint effects of supplement use and timing of use on SPB, we further classified the women into 6 groups according to both type of supplement used and starting time of consumption (Table 3). As Table 3 shows, except for gestational week, body mass index at enrollment, and type of supplement consumed, the 6 study groups were similar with respect to baseline characteristics. The mean gestational age at enrollment was 16 weeks in all 3 intervention groups of participants enrolled during or after the 12th week of pregnancy, and it was 8 weeks in all 3 intervention groups of participants enrolled before the 12th week of pregnancy. The small difference in body mass index between women enrolled before the 12th gestational week and women enrolled in the 12th gestational week or later was due to weight gain during pregnancy.

Table 4 presents the impact of the timing of enrollment and consumption on risk of SPB. Women who started consuming FA, IFA, and MMN supplements before the 12th week of gestation had significantly lower SPB incidence (4.6%, 4.2%, and 3.9%, respectively) than those who started consumption during the 12th week of gestation or later (6.9%, 7.2%, and 6.4%, respectively). Compared with women who started taking supplements in the 12th gestational week or later, women who started consuming FA, IFA, and MMN before the 12th week of gestation all showed a significantly decreased risk of SPB. Early consumption of FA, IFA, or MMN produced a 41%–45% reduction in the risk of SPB. We further examined whether there were differences in the protective effect of consumption timing for early or late SPB subtypes. We found that earlier consumption of micronutrients was significantly associated with late SPB but not with early SPB.

DISCUSSION

In this large, double-blind randomized controlled trial of prenatal supplementation conducted in rural areas of northern China, supplementation with IFA or MMN, as compared with FA, was not associated with a significantly decreased risk of SPB in general or of any subtype of SPB (early or late). However, we found a significantly reduced risk of SPB associated with early antenatal enrollment and consumption of micronutrients. Within each supplement group, consuming any micronutrients during the first trimester of pregnancy was associated with a 41%–45% reduction in the incidence of SPB as compared with later consumption.

With the increasingly widespread use of prenatal MMN supplements worldwide, there is interest in whether prenatal supplementation with MMN provides benefits beyond those conferred by IFA or FA. Numerous observational studies have suggested a protective effect of MMN on preterm birth (8–13). The findings of these studies are supported by the possible mechanism of the stronger antioxidant action of MMN. Oxidative stress is a contributing factor for tissue injury through formation of free radicals and reactive oxygen/nitrogen species, leading to increased levels of inflammatory cytokines, which can result in

preterm birth. Women in preterm labor have diminished antioxidant ability to defend against oxidative stress-induced damage (15, 16). Many micronutrients in MMN supplements, such as vitamins C, D, and E, selenium, zinc, and copper, are antioxidants. They scavenge free radicals in the aqueous phase or act in vivo to prevent the formation of lipid peroxides and thus protect cell membranes (17, 18). Therefore, relative to FA or IFA, MMN may provide a stronger antioxidant effect and the protective effect of reducing vasoconstriction and/or organ damage. Low vitamin C, vitamin D, selenium, zinc, and copper levels in maternal blood during early gestation or in the placenta have been associated with preterm birth (19, 20).

However, several large observational studies have not shown an association between antioxidants and micronutrients and preterm birth in high-resource settings (21, 22). Since the design of the United Nations/World Health Organization MMN supplement for pregnant and lactating women (UNIMMAP), a series of efficacy trials have been conducted to examine the effects of maternal MMN supplements on pregnancy outcomes as compared with IFA or FA. The majority of studies have compared MNN with IFA, and meta-analyses of these trials have not found a significant effect of MMN supplementation on preterm birth. Few of these trials have examined the effect of MMN relative to FA alone (4, 5). Our previous analysis (6) and a randomized controlled trial carried out in rural western China (23) both examined the effect of MMN and IFA relative to FA alone on preterm birth, and neither found a significant effect of either MMN or IFA. However, the subjects in the 2 studies included only liveborn infants at the 28th gestational week or above, and the studies did not examine the effect of micronutrients on different subtypes of preterm birth. This post hoc secondary analysis demonstrated that consumption of MMN or IFA supplements during pregnancy did not provide additional protective effects against SPB, or against early or late SPB, relative to FA alone. In the current analysis, we excluded the medically complicated cases of preterm delivery, considering the small number of such cases (n = 71 for each of the 3 subgroups) and the etiological heterogeneity involved with SPB. The most common obstetrical complication was gestational hypertension. The overall rate of gestational hypertension was 7.1% in the FA group, 6.3% in the IFA group, and 6.3% in the MMN group; there was no statistical difference between the supplement groups. However, preeclampsia could not be assessed, because there was no information on proteinuria.

Early preterm birth has been reported to be the leading cause of neonatal mortality (24). A Chinese nationwide survey showed that early preterm birth contributed to 57.9% of preterm neonatal deaths (25). In addition, survivors of early preterm birth incur immediate medical morbidity and long-term neurological impairment and pulmonary disorders (26). Some observational studies have suggested that use of MMN supplements was associated with a greater risk reduction for early preterm birth than for late preterm birth (8–10, 13). In a randomized controlled trial of Tanzanian women infected with human immunodeficiency virus, multivitamin supplementation decreased the risk of early preterm birth by 39% relative to the placebo (without any micronutrient) (13). However, in our trial, we did not find an association of supplement group with risk of either early or late preterm birth.

The timing of enrollment in prenatal care and the start of supplementation is of interest because of the critical time window for the development of the placenta and fetus. In our

study, within each supplement group, women who started consuming the supplement before the 12th week of gestation had a 41%–45% reduction in risk of SPB relative to the women who started consumption in the 12th gestational week or later. Although studies are scarce, a healthy diet starting in early pregnancy, or before pregnancy, is important for the prevention of several adverse pregnancy outcomes (27, 28). For preterm birth, studies suggest that the protective effect of MMN is most apparent among women who take MMN supplements before pregnancy or during early pregnancy (8–10, 12, 14). Two large cohort studies also showed that FA supplementation before or during early pregnancy had a protective effect against SPB (10, 14). In fact, duration of pregnancy has been hypothesized to be the ultimate consequence of conditions existing in the very earliest stages of pregnancy (10).

A limitation of our study is that we could not determine the factors that contributed to the protective effect of early enrollment. In addition to earlier exposure to supplements, women who enrolled in the study earlier consumed more pills and had earlier access to antenatal care. Although women who enrolled early had the same demographic characteristics as women who enrolled later, there may have been other differences that we could not account for (e.g., health-care-seeking behavior, access to care, and diet). In addition, early enrollees consumed more pills than later enrollees; thus, the protective effect of earlier consumption could also reflect the higher accumulated dosage. Another limitation was the relatively small sample size for some of the subgroups, which resulted in less precision for some results. Because of the definition of preterm birth, we had to exclude some postrandomization losses occurring before 20 gestational weeks. To estimate the effects of this exclusion on the main results for the 3 randomized supplement groups, we further analyzed the proportions of excluded individuals between the 3 groups. We did not find a significant difference in the percentages of excluded individuals between the 3 groups (373 pregnancies (6.0%) for the FA group, 332 pregnancies (5.3%) for the IFA group, and 352 pregnancies (5.6%) for the MMN group; $P > 0.05$).

Our estimation of gestational age was based on maternal self-recorded date of the last menstrual period, which would have been less accurate than determination by ultrasonography. Because we were concerned about the accuracy of the date of the last menstrual period, we required menstrual monitoring for 2 months prior to enrollment. In addition, all participants underwent a pregnancy test within 1–2 weeks after a missed menstrual period. The combination of self-monitoring of menstruation, monthly visits by village health workers, and timely laboratory confirmation of pregnancy allowed early detection of pregnancy and accurate recording of the dates of last menstrual periods. In addition, because women with moderate or severe anemia (hemoglobin level ≤ 10.0 g/dL) were excluded from enrollment, our study may have underestimated the effect of iron or MMN supplementation in populations with higher levels of anemia. The overall rate of preterm birth in our study population was lower than that in many other countries. Relative to other Chinese rural areas, our population was well-educated and had good access to medical care. Nearly all study newborns (99.7%) were delivered at a medical clinic in the township or district hospitals. Because of enrollment criteria, all participants were at least 20 years of age and were either nonanemic or only mildly anemic. Maternal anemia before pregnancy or in early pregnancy has been associated with increased risk of preterm birth

(29, 30). Therefore, the results of our study may not be generalizable to disadvantaged populations with high levels of anemia and poor access to medical care.

Our study had several strengths. The study was individual-based and had a double-blind, randomized controlled design, and the baseline characteristics were well-balanced across groups. To our knowledge, this is one of the largest randomized controlled trials to have examined the effect of MMN on pregnancy outcomes. Supplement-taking was confirmed monthly through home visits by health workers, and compliance was very high (median compliance reached 97%). All pregnancy outcomes, including preterm birth, were ascertained by active community surveillance, review of vital registration certificates, and review of hospital records. Fewer than 1% of the enrolled participants were lost to follow-up. The data were managed by the electronic reproductive health system, which possessed a powerful error-checking function and greatly lowered the number of entry errors in each township or county hospital.

In conclusion, our results indicate that daily supplementation with IFA or MMN, versus FA, during pregnancy was not associated with a significantly decreased risk of SPB. However, consumption of any supplement (FA or FA-containing micronutrients) before the 12th week of gestation produced a 41%–45% reduction in the risk of SPB in comparison with later consumption.

ACKNOWLEDGMENTS

This study was supported by a cooperative agreement between the Peking University Health Science Center and the US Centers for Disease Control and Prevention and by the National Natural Science Foundation of China (grants 81673177 and 81373014).

We are grateful to the hundreds of health-care workers from Yuanshi, Mancheng, Xianghe, Fengrun, and Laoting counties (Hebei Province, China) for their support. We thank the members of the data safety and monitoring board at the Institute of Reproductive and Child Health/Ministry of Health Key Laboratory of Reproductive Health (Peking University Health Science Center, Beijing, China) and all other staff who participated in the project at the Peking University Health Science Center and the Centers for Disease Control and Prevention.

Abbreviations:

FA	folic acid
IFA	iron + folic acid
MMN	multiple micronutrients
SPB	spontaneous preterm birth
UNIMMAP	United Nations Multiple Micronutrient Antenatal Preparation

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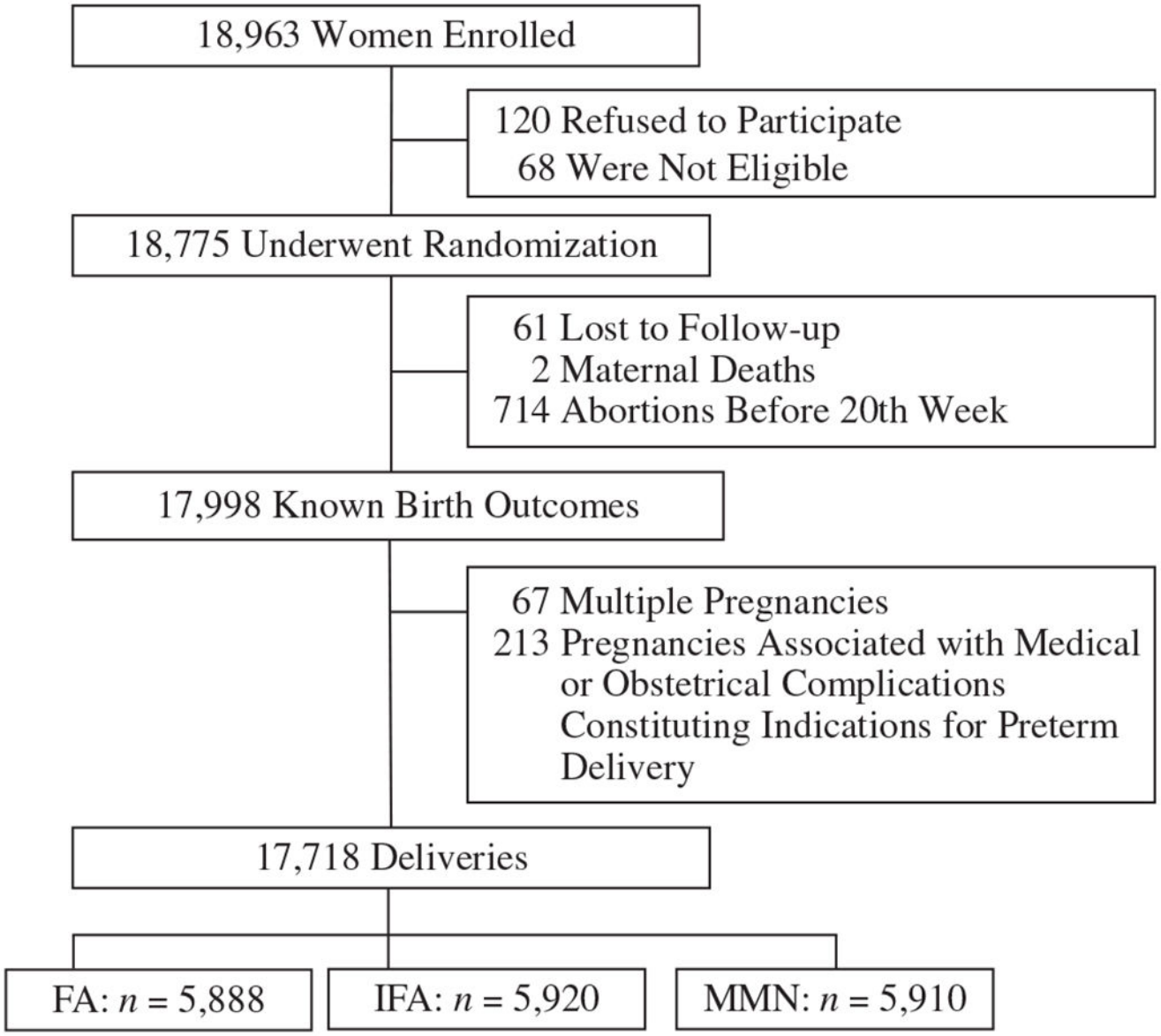

Figure 1.
Selection of participants for a study of prenatal micronutrient supplementation and spontaneous preterm birth, northern China, 2006–2009. FA, folic acid; IFA, iron + folic acid; MMN, multiple micronutrients.

Table 1.

Baseline Maternal Characteristics and Compliance in a Study of Prenatal Micronutrient Supplementation and Spontaneous Preterm Birth, Northern China, 2006–2009

Characteristic	Supplement Group								
	FA (*n* = 5,888)			IFA (*n* = 5,920)			MMN (*n* = 5,910)		
	Mean (SD)	No. of Women	%	Mean (SD)	No. of Women	%	Mean (SD)	No. of Women	%
Age at pregnancy, years	23.4 (2.9)			23.4 (2.8)			23.3 (2.7)		
Height, cm	160.1 (4.5)			160.2 (4.5)			160.2 (4.5)		
Body mass index[a] at enrollment	22.3 (2.8)			22.3 (2.8)			22.3 (2.9)		
Education									
Primary school or lower		1,089	18.5		1,064	18.0		1,067	18.1
Junior high school		4,709	80.0		4,755	80.3		4,754	80.4
High school or higher		90	1.5		101	1.7		89	1.5
Ethnicity									
Han		5,813	98.7		5,856	98.9		5,841	98.8
Other		75	1.3		64	1.1		69	1.2
Occupation									
Farmer		5,346	90.8		5,393	91.1		5,380	91.0
Other		542	9.2		527	8.9		530	9.0
Gestational week at enrollment									
<12		3,080	52.3		3,054	51.6		3,105	52.5
≥12		2,808	47.7		2,866	48.4		2,805	47.5
Mean gestational week at enrollment	12.1 (4.5)			12.1 (4.5)			12.1 (4.6)		
Median level of compliance[b]			97.0			97.0			97.0
Median no. of supplements consumed		184			183			183	

Abbreviations: FA, folic acid; IFA, iron + folic acid; MMN, multiple micronutrients; SD, standard deviation.

[a] Weight (kg)/height $(m)^2$.

[b] Compliance was calculated as the number of supplements consumed divided by the number of days on which supplements were expected to be consumed.

Table 2.

Incidence of Spontaneous Preterm Birth According to Use of Micronutrient Supplements Among Pregnant Women in Northern China, 2006–2009

SPB Category	Supplement Group									
	FA (n = 5,888)[a]		IFA (n = 5,920)				MMN (n = 5,910)			
	No. of Cases	Incidence[b], %	No. of Cases	Incidence[b], %	RR	95% CI	No. of Cases	Incidence[b], %	RR	95% CI
All SPBs (20–36 weeks)	335	5.7	334	5.6	0.99	0.85, 1.16	302	5.1	0.89	0.76, 1.05
Late SPBs (32–36 weeks)	287	4.9	288	4.9	1.00	0.84, 1.18	262	4.5	0.90	0.76, 1.07
Early SPBs (20–31 weeks)	48	0.9	46	0.8	0.95	0.63, 1.43	40	0.7	0.83	0.54, 1.26

Abbreviations: CI, confidence interval; FA, folic acid; IFA, iron + folic acid; MMN, multiple micronutrients; RR, risk ratio; SPB, spontaneous preterm birth.

[a]Reference group.

[b]Calculation of the incidence of certain types of preterm birth did not include other subtypes of preterm birth in the denominator.

Table 3.

Baseline Maternal Characteristics and Compliance in a Study of Prenatal Micronutrient Supplementation and Spontaneous Preterm Birth, by Timing of Study Enrollment and Supplement Use, Northern China, 2006–2009

Characteristic	Enrollment at ≥12 Gestational Weeks									Enrollment at <12 Gestational Weeks								
	FA (*n* = 2,808)			IFA (*n* = 2,866)			MMN (*n* = 2,805)			FA (*n* = 3,080)			IFA (*n* = 3,054)			MMN (*n* = 3,105)		
	Mean (SD)	No. of Women	%	Mean (SD)	No. of Women	%	Mean (SD)	No. of Women	%	Mean (SD)	No. of Women	%	Mean (SD)	No. of Women	%	Mean (SD)	No. of Women	%
Gestational week at enrollment	16.1 (2.6)			16.2 (2.5)			16.2 (2.5)			8.3 (2.1)			8.3 (2.1)			8.3 (2.1)		
Median level of compliance[a]			97.0			97.0			97.0			97.0			97.0			97.0
Median no. of supplements consumed		154			154			152			209			208			208	
Age at pregnancy, years	23.4 (2.9)			23.4 (2.9)			23.3 (2.8)			23.4 (2.8)			23.4 (2.8)			23.4 (2.8)		
Height, cm	160.1 (4.4)			160.1 (4.5)			160.1 (4.5)			160.0 (4.6)			160.3 (4.6)			160.2 (4.5)		
Body mass index[b] at enrollment	22.6 (2.9)			22.4 (2.8)			22.5 (2.8)			22.0 (2.7)			22.1 (2.9)			22.1 (2.9)		
Education																		
Primary school or lower		526	18.7		494	17.2		479	17.1		563	18.3		570	18.7		588	18.9
Junior high school		2,247	80.0		2,323	81.1		2,279	81.2		2,462	79.9		2,432	79.6		2,475	79.7
High school or higher		35	1.2		49	1.7		47	1.7		55	1.8		52	1.7		42	1.4
Ethnicity																		
Han		2,779	99.0		2,835	98.9		2,777	99.0		3,034	98.5		3,021	98.9		3,064	98.7
Other		29	1.0		31	1.1		28	1.0		46	1.5		33	1.1		41	1.3
Occupation																		
Farmer		2,552	90.9		2,618	91.3		2,557	91.2		2,794	90.7		2,775	90.9		2,823	90.9
Other		256	9.1		248	8.7		248	8.8		286	9.3		279	9.1		282	9.1

Abbreviations: FA, folic acid; IFA, iron + folic acid; MMN, multiple micronutrients; SD, standard deviation.

[a]Compliance was calculated as the number of supplements consumed divided by the number of days on which supplements were expected to be consumed.

[b] Weight (kg)/height (m)^2.

Table 4.

Risk of Spontaneous Preterm Birth According to Timing of Study Enrollment and Use of Micronutrient Supplements Among Pregnant Women in Northern China, 2006–2009

Timing of Enrollment and Supplement Group	SPB Category											
	All SPBs (20–36 Weeks)				Late SPBs (32–36 Weeks)				Early SPBs (20–31 Weeks)			
	No. of Cases	Incidence[a], %	RR	95% CI	No. of Cases	Incidence[a], %	RR	95% CI	No. of Cases	Incidence[a], %	RR	95% CI
Enrollment at ≥12 gestational weeks												
FA	193	6.9	1	Referent	171	6.1	1	Referent	22	0.8	1	Referent
IFA	207	7.2	1	Referent	186	6.5	1	Referent	21	0.8	1	Referent
MMN	180	6.4	1	Referent	158	5.7	1	Referent	22	0.8	1	Referent
Enrollment at <12 gestational weeks												
FA	142	4.6	0.66	0.52, 0.82	116	3.8	0.60	0.47, 0.77	26	0.9	1.05	0.60, 1.86
IFA	127	4.2	0.59	0.47, 0.74	102	3.4	0.53	0.41, 0.68	25	0.8	1.02	0.57, 1.81
MMN	122	3.9	0.55	0.44, 0.70	104	3.4	0.53	0.42, 0.68	18	0.6	0.72	0.38, 1.34

Abbreviations: CI, confidence interval; FA, folic acid; IFA, iron + folic acid; MMN, multiple micronutrients; RR, risk ratio; SPB, spontaneous preterm birth.

[a]Calculation of the incidence of certain types of preterm birth did not include other subtypes of preterm birth in the denominator.