HHS Public Access

Author manuscript

J Nutr. Author manuscript; available in PMC 2022 April 25.

Published in final edited form as:

J Nutr. 2014 June ; 144(6): 943–948. doi:10.3945/jn.113.189894.

Iron-Containing Micronutrient Supplementation of Chinese Women with No or Mild Anemia during Pregnancy Improved Iron Status but Did Not Affect Perinatal Anemia[2]

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Abstract

Universal prenatal daily iron–folic acid (IFA) and multiple micronutrient (MM) supplements are recommended to reduce the risk of low birth weight, maternal anemia, and iron deficiency (ID) during pregnancy, but the evidence of their effect on iron status among women with mild or no anemia is limited. The aim of this study was to describe the iron status [serum ferritin (SF), serum soluble transferrin receptor (sTfR), and body iron (BI)] before and after micronutrient supplementation during pregnancy. We examined 834 pregnant women with hemoglobin > 100 g/L at enrollment before 20 wk of gestation and with iron measurement data from a subset of a randomized, double-blind trial in China. Women were randomly assigned to take daily 400 μg of folic acid (FA) (control), FA plus 30 mg of iron, or FA, iron, plus 13 additional MMs provided before 20 wk of gestation to delivery. Venous blood was collected in this subset during study enrollment (before 20 wk of gestation) and 28–32 wk of gestation. We found that, at 28–32 wk of gestation, compared with the FA group, both the IFA and MM groups had significantly lower prevalence of ID regardless of which indicator (SF, sTfR, or BI) was used for defining ID. The prevalence of ID at 28–32 wk of gestation for IFA, MM, and FA were 35.3%, 42.7%, and 59.6% by using low SF, 53.6%, 59.9%, and 69.9% by using high sTfR, and 34.5%, 41.2%, and 59.6% by using low BI, respectively. However, there was no difference in anemia prevalence (hemoglobin <110 g/L) between FA and IFA or MM groups. We concluded that, compared with FA alone, prenatal IFA and MM supplements provided to women with no or mild anemia improved iron status later during pregnancy but did not affect perinatal anemia. This trial was registered at clinicaltrials.gov as NCT00137744.

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[2]Author disclosures: Z. Mei, M. K. Serdula, J.-m. Liu, R. C. Flores-Ayala, L. Wang, R. Ye, and L. M. Grummer-Strawn, no conflicts of interest,

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Introduction

The WHO recommends that pregnant women take daily oral iron–folic acid (IFA)[5] supplementation as part of antenatal care to reduce the risk of low birth weight, maternal anemia, and iron deficiency (ID) (1). Meta-analyses of randomized controlled trials indicate that daily prenatal IFA supplementation prevents ID and anemia (2). Multiple micronutrient (MM) supplements had the same effect on hemoglobin and iron status indicators as iron with or without folic acid (FA) (3). However, the evidence is limited on the effect of prenatal IFA or MM supplementations among women without anemia or those with mild anemia.

A meta-analysis conducted by Peña-Rosa et al. (2) found that, among 7 trials that included iron indicators as the outcome (1256 women), women in groups receiving iron as part of their supplements were less likely to have ID at term (RR: 0.43; 95% CI: 0.27, 0.66). Five of the 7 studies recruited women who did not have anemia at the start of supplementation. However, all 7 studies on iron status had small sample sizes (<150 in the iron group), and all had only 2 treatment groups (iron group and non-iron placebo group). In the same meta-analysis, Peña-Rosa et al. included 14 trials with hemoglobin measured; 13% of those (among 2199 women) who received daily iron supplements during pregnancy had anemia at term compared with 36% who did not take iron (RR: 0.30; 95% CI: 0.19, 0.46).

A pooled analysis conducted by Allen and Peerson (3) found that, among 13 studies, women who received MM supplements had increased hemoglobin concentration and ferritin to the same extent as those supplemented with iron with or without FA. However, all the 13 studies were conducted in developing countries with a high prevalence of anemia at the start of supplementation.

A large randomized control trial of prenatal supplementation with FA, IFA, and MM in China conducted among an educated population with good access to health care and low amounts of anemia at enrollment (~5–6%) (4) allowed us the opportunity to explore the effect of iron-containing micronutrient supplementation on the iron and hemoglobin status of women later during pregnancy. This study examines the iron status before and after iron-containing micronutrient supplementation during pregnancy among the 3 treatment groups, in a population without anemia or only mild anemia.

Participants and Methods

Study population and sample selection.

The trial took place in 5 rural counties in Hebei Province, China. Eligible pregnant women were enrolled from May 2006 to April 2009 and individually randomly assigned in a 1:1:1 ratio to take a daily supplement containing FA (400 μg) (control), IFA (FA plus 30 mg of iron), or MM formula from the United Nations International Multiple Micronutrient Preparation (FA, 30 mg of iron, plus 13 additional MMs) provided before 20 wk of gestation to delivery. Women were followed monthly from early pregnancy through delivery and

[5]Abbreviations used: BI, body iron; CRP, C-reactive protein; FA, folic acid; ID, iron deficiency; IFA, iron–folic acid; MM, multiple micronutrient; SF, serum ferritin; sTfR, serum soluble transferrin receptor.

at 4–8 wk postpartum. Their infants were followed monthly from birth until 1 y of age. The following were inclusion criteria for the pregnant women: *1*) recorded dates of their menstruation for ≥2 mo before they became pregnant; *2*) nulliparous; *3*) aged ≥20 y; *4*) ≤20 wk of gestation; *5*) legally competent; *6*) had not consumed iron supplements or other micronutrient supplements (other than FA) in the previous 6 mo; *7*) hemoglobin ≥ 100 g/L; *8*) resided in and received prenatal care in 1 of 5 counties; and *9*) consented to participate. Randomization of individual women was stratified by county and random block sizes of 3, 6, and 9 to ensure geographical balance with an approximately equal distribution of treatments within and across study counties. A statistician external to the study randomly assigned 10 4-digit lot numbers to each of the 3 types of supplements and generated the assignment list for each county proportional to the expected number of participants. Within each county, within each block, lot numbers were randomly assigned using RANUNI in SAS statistical software. Aside from the statistician and a pharmaceutical engineer who ensured allocation of lot numbers to the correct supplement formulations, all others were masked to the identity of the supplements. The Data Safety Monitoring Board met 4 times during the study and reviewed the results according to supplement group, masked to supplement allocation.

In this study, 18,775 nulliparous pregnant women with hemoglobin > 100 g/L were enrolled and randomly assigned before 20 wk gestational age and followed monthly through delivery and at 4–8 wk postpartum (4). The primary outcome of this trial was perinatal mortality. Secondary outcomes included neonatal and infant mortality, preterm delivery, birth weight, birth length, gestational duration, and maternal hemoglobin concentration and anemia (hemoglobin < 110 g/L). Mean compliance was >91% for all 3 treatment groups. Detailed information on this trial was published previously (4).

To understand the physiologic mechanisms underlying any beneficial or deleterious treatment effects observed during the trial, venous blood was collected from a subsample of mothers at 2 points during pregnancy during enrollment of the study before 20 wk of gestation and at 28–32 wk of gestation. This subsample of mothers was only enrolled in 2 of the 5 study sites (Mancheng and Xianghe counties). A modified consent form was used during the enrollment of the subsample from March 2008 to February 2009, and the study protocol was approved by the Institutional Review Boards of the U.S. CDC and the Peking University Health Science Center, China.

Standardized training including cold chain procedures was conducted. The blood samples were centrifuged [3000 rpm (1500 × *g*); 10 min], and serum was separated from the RBCs within 2 h after collection, then portioned into frozen tubes, and stored at −20°C for 1 wk at field sites. Serum samples were shipped on dry ice to the laboratory of the National Center of Maternal and Infant Health, Peking University, and then stored at −80°C until analysis could be performed. Blood samples were collected from 1145 women at enrollment and 834 at 28–32 wk of gestation. For this analysis, we only included women with both blood samples collected (n = 834). Details on sample size by study groups are shown in Figure 1.

Laboratory analysis and anthropometric measurement.

Serum ferritin (SF) (in micrograms per liter) was measured by an electrochemiluminescence immunoassay (Roche Elecsys-E 170; Roche Diagnostics). Aliquots from a pool of quality control samples were prepared from serum samples with low, medium, and high concentrations of SF. The CVs of 3 concentrations for SF in these quality control specimens were 3.5%, 2.7%, and 3.2%, and the biases of 3 concentrations were 0.2%, 7.8%, and 1.2%, respectively. The abnormal value for SF was defined as <12 μg/L (5).

Serum soluble transferrin receptor (sTfR) (in micrograms per liter) was determined by using a sandwich ELISA (Labsystem Multiscan MS type 352). The following antigen and antibodies were used as purchased: sTfR (catalog No. 8Tr56; Hytest), monoclonal mouse anti-human sTfR (catalog No. 4Tr26; Hytest), and monoclonal mouse anti-human HRP-conjugated sTfR (catalog No. 4Tr26-c; Hytest). Aliquots from a pool of quality control samples were prepared from serum samples with a low, medium, and high concentration of sTfR. The CVs of 3 concentrations for sTfR in these quality control specimens were 8.7%, 6.0%, and 8.6%, respectively, and the biases were not given for analyses for which a standard reference material is not available. The abnormal value for sTfR was defined as >4.4 μg/L (6).

Body iron (BI) was calculated from sTfR and SF concentrations by using a formula from Cook and colleagues (7,8) after converting Roche sTfR concentrations to those equivalent to the assay by Flowers et al. (9) used in the development of the BI model (7,8):

$$\text{Body iron(mg/kg)} = -[\log 10(\text{sTfR} \times 1000/\text{ferritin}) - 2.8229]/0.1207.$$

To convert the Roche sTfR concentrations to that equivalent to the assay by Flowers et al. (9), we applied a conversion equation derived from a previous comparison (10) of the 2 assays ($n = 40$):

$$\text{Flowers sTfR} = 1.5 \times \text{Roche sTfR} + 0.35 \text{ mg/L}.$$

We used the original Roche ferritin concentrations for the BI calculation because a previous comparison of the Roche ferritin assay with the ELISA method used to develop the BI model (7,8) indicated that these 2 methods generated similar values (11). An abnormal value for BI was defined as <0 mg/kg (7,8).

Serum C-reactive protein (CRP) (in milligrams per liter) was determined by using a sandwich ELISA (Labsystem Multiscan MS type 352). The antigen and antibodies were as follows: CRP (catalog No. 8C72; Hytest), monoclonal mouse anti-human CRP (catalog No. 4C28; Hytest), and monoclonal mouse anti-human HRP-conjugated CRP (catalog No. 4C28C; Hytest). Aliquots from a pool of quality control samples were prepared from serum samples with a low, medium, and high concentration of serum CRP. The CVs of 3 concentrations for serum CRP in these quality control specimens were 5.5%, 4.8%, and 6.0%, and the biases of 3 concentrations were 14.6%, 9.0%, and 1.0%, respectively. The abnormal value for CRP was defined as >5 mg/L (12).

Hemoglobin concentration was measured from venous whole blood by using the HemoCue system at enrollment and at 28–32 wk of gestation. Maternal anemia was defined as an hemoglobin concentration < 110.0 g/L (5).

Maternal weight was measured at enrollment using an electronic scale (BW 150; UWE) with precision to the nearest 50 g, and height was measured at enrollment by a collapsible height board to the nearest 0.1 cm.

Statistical analysis.

First, we explored whether inflammation status measured by CRP may have contributed to differences in the 3 treatment groups by comparing the inflammation status across the treatment groups.

Second, we log-transformed SF [ln(ferritin)] and sTfR [ln(sTfR)] to normalize the distributions, because SF and sTfR concentrations were positively skewed (13,14). We then plotted the log-transformed sTfR and SF distributions for pregnant women for both baseline and follow-up values. Finally, we calculated the SF and sTfR geometric means and the percentages of abnormal value at baseline and follow-up. For the distribution of BI and hemoglobin, arithmetic means were used because both total BI and hemoglobin were not skewed distributed, unlike sTfR or SF (7,8). The percentage of abnormal values for BI and hemoglobin were also calculated.

We used SAS statistical software (version 9.3; SAS) for all analyses, and all analyses were stratified by 3 treatment groups (FA, IFA, and MM). To compare baseline demographic and maternal characteristics at enrollment by study group, χ^2 tests were used to examine statistical differences in categorical variables and ANOVA to examine differences in means among study groups. Also, the same tests were used to compare differences in the refusal by treatment group. For biochemical indicators, we used generalized linear models to test the difference at follow-up for the means, and we used generalized estimating equation models to examine the difference at follow-up for the prevalence adjusted by baseline amount of each indicator and gestational age. McNemar's test was used to test the difference in the percentages between baseline and follow-up, and paired *t* tests were used to test differences in means. Study participants' baseline characteristics are reported as means ± SDs or percentages. All iron biomarkers are reported as means (95% CIs) or geometric means (95% CIs). Significance was set at $P < 0.05$.

Results

Among the 1994 pregnant women enrolled from March 2008 to February 2009, 851 remained in the main study but refused to participate in venous blood collection at enrollment. Of the 1143 women who had a venous blood sample collected at enrollment, 309 refused venous blood collection at 28–32 wk of gestation (Fig. 1). Refusal rates were not statistically different by treatment group at enrollment or at 28–32 wk of gestation ($P > 0.1$). There were no differences in basic characteristics (maternal age, education, ethnicity, occupation, BMI, height, gestational age, and baseline hemoglobin) between women who participated and refused ($P > 0.05$).

The geometric means of CRP by 3 treatment groups at baseline and follow-up are shown in Table 1. All the participants included in our final analyses as the mean CRPs by 3 treatment groups were comparable at both baseline and follow-up, although the mean CRPs at follow-up were significantly higher than at baseline (Table 1).

The baseline characteristics between groups were balanced across supplement groups (Table 2). The mean maternal age was 23.3 ± 2.4 y, gestation at enrollment was 11.6 ± 4.5 wk, and hemoglobin was 121.8 ± 8.3 g/L. In addition, 97.8% of the women were Han ethnicity, 1.9% had primary or less education, and 91.1% were farmers. Only 5.6% of women had mild anemia (hemoglobin of 100–109 g/L) at baseline. No serious adverse effects were reported. The adverse effects were nausea, vomiting, or other mild gastrointestinal discomfort: 7 women in the FA group (2.5%) reported gastrointestinal discomfort, 6 (2.2%) in the IFA group, and 23 (8.4%) in the MM group ($P < 0.001$).

At baseline (<20 wk of gestation), SF geometric means were comparable among the 3 treatment groups. However, at 28–32 wk gestational age, although SF geometric means among all the 3 groups were significantly lower than at baseline, the SF geometric means in both the IFA and MM groups were significantly higher compared with the FA group even after adjusting for baseline SF and gestational age (Table 3). Consistent with these findings, the prevalence of ID defined by low SF was significantly lower in the IFA or MM groups compared with the FA group (Table 4). This indicates that it was not only a shift in the mean but also the entire distribution as seen in Figure 2A.

Similar to SF, the sTfR geometric means among the 3 groups did not differ at baseline. At follow-up, only the mean for the IFA group was significantly lower than the FA group (Table 3). However, both the IFA and MM groups had a significant reduction in the prevalence of ID defined by high sTfR (Table 4) even after adjustment for the baseline sTfR concentration and gestational age. The sTfR distribution also showed a shift of the entire distribution before and after the intervention (Figure 2B).

The patterns of BI from baseline to follow-up by 3 groups were similar to those of SF. The means in both the IFA and MM groups were significantly higher than that of the FA group (Table 3) after adjustment for baseline amounts. As shown in Figure 2C, the shift was a shift of the entire distribution before and after the intervention. In addition, the prevalence of ID defined by low BI from the FA group was significantly higher than that of the IFA or MM groups (Table 4).

In contrast to the patterns observed for SF, sTfR, and BI, the mean hemoglobin of the 3 treatment groups was not significantly different at baseline and was also not significantly different at follow-up. However, each group had an increased mean at follow-up compared with baseline (Table 3). There were no significant changes in the prevalence of anemia from baseline to follow-up for any of the 3 groups. However, at follow-up, although the prevalence of anemia did not significantly differ between the FA and IFA or MM groups, the prevalence of anemia was higher in the IFA group compared with the MM group after adjustment for baseline amounts (Table 4).

Discussion

In this primarily rural population without anemia living north of Beijing, we found that, compared with FA alone, prenatal supplementation with IFA or MM improved iron status in later pregnancy but did not affect perinatal anemia.

Our trial was designed to address differences in perinatal outcomes among women who did not have anemia or only mildly anemia. Although we excluded women with moderate or severe anemia (<100 g/L), we did not exclude women with high hemoglobin concentrations, which is consistent with international guidelines for universal iron supplementation in pregnant women as recommended by the WHO (1). Although we did not have any biomarker on iron toxicity, trial participants were monitored monthly for compliance and side effects. The Data Safety Monitoring Board, formed by 4 well-known iron experts and 1 statistician, met 4 times during the study to review the preliminary results, including side effects. Although no serious adverse effects were reported in our study, women who participated in MM group reported significant higher gastrointestinal discomfort compared with the IFA or FA group. In future studies, it would be better to include a biomarker for iron toxicity or overload in women who are not anemic at baseline but are receiving iron supplementation.

In contrast to most previous trials of MM supplementation during pregnancy (3), our study population was primarily without anemia (>93%) or had only mild anemia. Although predominantly rural (91% were farmers), nearly all women had at least a secondary education, and few were undernourished as measured by anthropometry. In addition, having monitored their menstrual cycle for ≥2 mo before enrollment to calculate the exact gestation age, women were cognizant of their last menstrual period and prenatal health. Once enrolled, women were followed monthly and delivered in the hospital. This large trial found that adding iron, with or without MMs, made little difference to perinatal deaths, neonatal deaths, infant deaths, birth weight, and preterm births but reduced the risk of anemia in late pregnancy compared with FA alone (4). However, the effect of reducing anemia was small in absolute terms (7.7% of women anemic by the third trimester who took FA alone compared with 5.5% of women who were anemic who took IFA or MMs) because women with hemoglobin < 100 g/L at baseline were excluded from this study (4). This analysis, which is a subset of the large trial with biochemical measurement, found no difference in anemia among the 3 groups at baseline but at follow-up, and although the 2 treatment groups (IFA and MM) were not different from the control group (FA), they were different from each other (Table 4). However, mean hemoglobin increased at follow-up for all the groups compared with baseline (Table 3).

Our results are similar to the findings from the review by Peña-Rosas et al. (2), who reported that women receiving iron as part of supplements are less likely to have ID at term. Five of the 7 studies included in the review (2) excluded women with anemia at the start of supplementation, but all the studies only had 2 study arms (iron group and non-iron placebo group). Our study, which excluded women with hemoglobin < 100 g/L from the beginning but randomly assigned to 3 study arms (FA, IFA, and MM groups) with large sample size, confirmed with both SF and sTfR measurements that, even in a population without anemia

or one with mild anemia, women taking IFA or MM during pregnancy will still improve their iron status in their late pregnancy compared with FA alone.

The review by Allen and Peerson (3) found that women receiving MM supplements increased hemoglobin concentration and ferritin to the same extent as supplementation with iron with or without FA. However, most of the previous studies included in the reviews had only 1 iron measure, and, in most cases, it was SF. SF is an acute-phase protein and could be affected by inflammation or infection. This is problematic for comparisons when the inflammation or infection rates are different among treatment groups. In contrast to SF, sTfR is not influenced or is only marginally influenced by the inflammatory response to infection (15). Our study measured CRP to account for the inflammation and measured both SF and sTfR and then calculated BI based on SF and sTfR. All 3 iron indicators confirmed that, compared with the FA group, both the IFA and MM groups had significantly lower prevalence of ID at 28–32 wk of gestation even after taking the baseline amount and gestational age into account (Table 4).

In summary, to the best of our knowledge, our study is the first large-scale double-blind individually randomized controlled trial to directly assess the impact of prenatal supplementation on perinatal iron status and anemia in population without anemia or with only mild anemia. The improvement in iron status with IFA and MM supplements among women without anemia or those with mild anemia provides additional support for universal iron supplementation to prevent maternal ID during late pregnancy.

Acknowledgments

Z.M. had full access to all of the data in this study, was responsible for the integrity of the data and the accuracy of the data analysis, and drafted the manuscript; and Z.M., M.K.S., J.-m.L., R.C.F.-A., L.W., R.Y., and L.M.G.-S. were responsible for the study concept and design, interpretation of the data, and critical revision of the manuscript. All authors read and approved the final version of the manuscript.

Supported by a cooperative agreement between Peking University Health Science Center and the CDC. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC.

Literature Cited

1. World Health Organization. Guideline: daily iron and folic acid supplementation in pregnant women. Geneva, Switzerland: WHO, 2012.
2. Peña-Rosas JP, De-Regil LM, Dowswell T, Viteri FE. Daily oral iron supplementation during pregnancy. Cochrane Database Syst Rev 2012; 12:CD004736. [PubMed: 23235616]
3. Allen LH, Peerson JM; Maternal Micronutrient Supplementation Study Group. Impact of multiple micronutrient versus iron-folic acid supplements on maternal anemia and micronutrient status in pregnancy. Food Nutr Bull 2009;30(Suppl 4):S527–32. [PubMed: 20120794]
4. Liu JM, Mei Z, Ye R, Serdula MK, Ren A, Cogswell ME. Micronutrient supplementation and pregnancy outcomes: double-blind randomized controlled trial in China. JAMA Intern Med 2013;173:276–82. [PubMed: 23303315]
5. Centers for Disease Control and Prevention. Recommendations to prevent and control iron deficiency in the United States. MMWR Recomm Rep 1998;47:1–29.
6. Kolbe-Busch S, Lotz J, Hafner G, Blanckaert NJ, Claeys G, Togni G, Carlsen J, Röddiger R, Thomas L. Multicenter evaluation of a fully mechanized soluble transferrin assay on the Hitachi and

Cobas Integra analyzers. The determination of reference ranges. Clin Chem Lab Med 2002;40:529–36. [PubMed: 12113300]

7. Cook JD, Flowers CH, Skikne BS. The quantitative assessment of body iron. Blood 2003;101:3359–64. [PubMed: 12521995]
8. Skikne BS, Flowers CH, Cook JD. Serum transferrin receptor: a quantitative measure of tissue iron deficiency. Blood 1990;75:1870–6. [PubMed: 2331526]
9. Flowers CH, Skikne BS, Covell AM, Cook JD. The clinical measurement of serum transferrin receptor. J Lab Clin Med 1989;114:368–77. [PubMed: 2677198]
10. Mirel LB, Curtin LR, Gahche J, Burt V. Characteristics of pregnant women from the 2001–06 National Health and Nutrition Examination Survey. Joint Statistical Meetings Proceedings, Government Statistics Section. Alexandria, VA: American Statistical Association; 2009:2592–602.
11. Cogswell ME, Looker AC, Pfeiffer CM, Cook JD, Lacher DA, Beard JL, Lynch SR, Grummer-Strawn LM. Assessment of iron deficiency in US preschool children and nonpregnant females of childbearing age: National Health and Nutrition Examination Survey 2003–2006. Am J Clin Nutr 2009;89:1334–42. [PubMed: 19357218]
12. Dati F, Schumann G, Thomas L, Aguzzi F, Baudner S, Bienvenu J, Blaabjerg O, Blirup-Jensen S, Carlström A, Petersen PH, et al. Consensus of a group of professional societies and diagnostic companies on guidelines for interim reference ranges for 14 proteins in serum based on the standardization against the IFCC/BCR/CAP reference material (CRM 470). Eur J Clin Chem Clin Biochem 1996;34:517–20. [PubMed: 8831057]
13. Akesson A, Bjellerup P, Berglund M, Bremme K, Vahter M. Serum transferrin receptor: a specific marker of iron deficiency in pregnancy. Am J Clin Nutr 1998;68:1241–6. [PubMed: 9846853]
14. Virtanen M, Siimes MA, Krusius T, Pettersson T, Teppo AM, Viinikka L. Evaluation of an ELISA test for determination of the serum transferring receptor. Demonstration of discordance between results obtained with two methods. Scand J Clin Lab Invest 1998;58:561–7. [PubMed: 9890339]
15. Beguin Y. Soluble transferrin receptor for the evaluation of erythropoiesis and iron status. Clin Chim Acta 2003;329:9–22. [PubMed: 12589962]

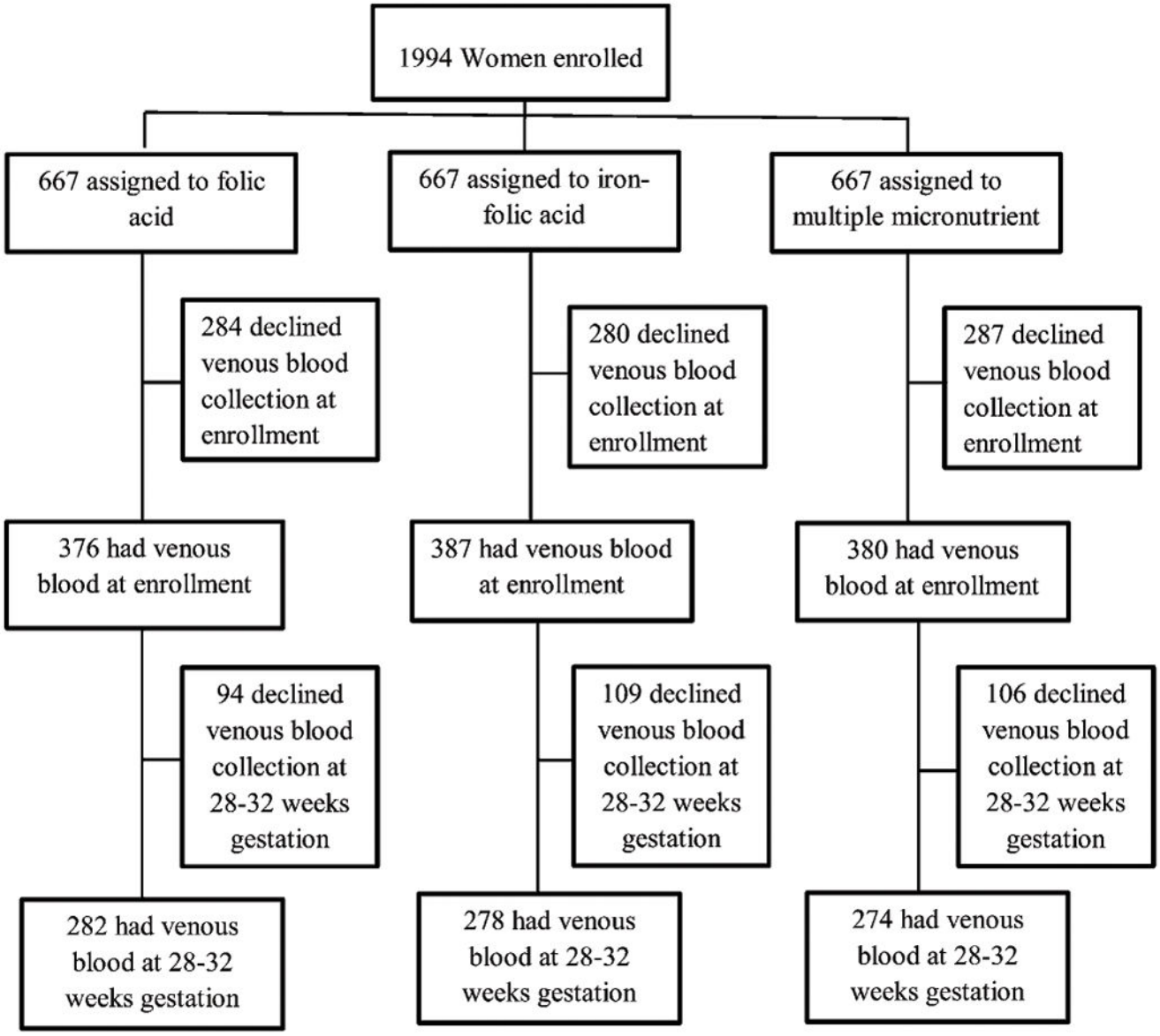

FIGURE 1.
Flowchart of participants in a randomized, double-blind study of pregnant women in China, 2008–2010, by intervention groups.

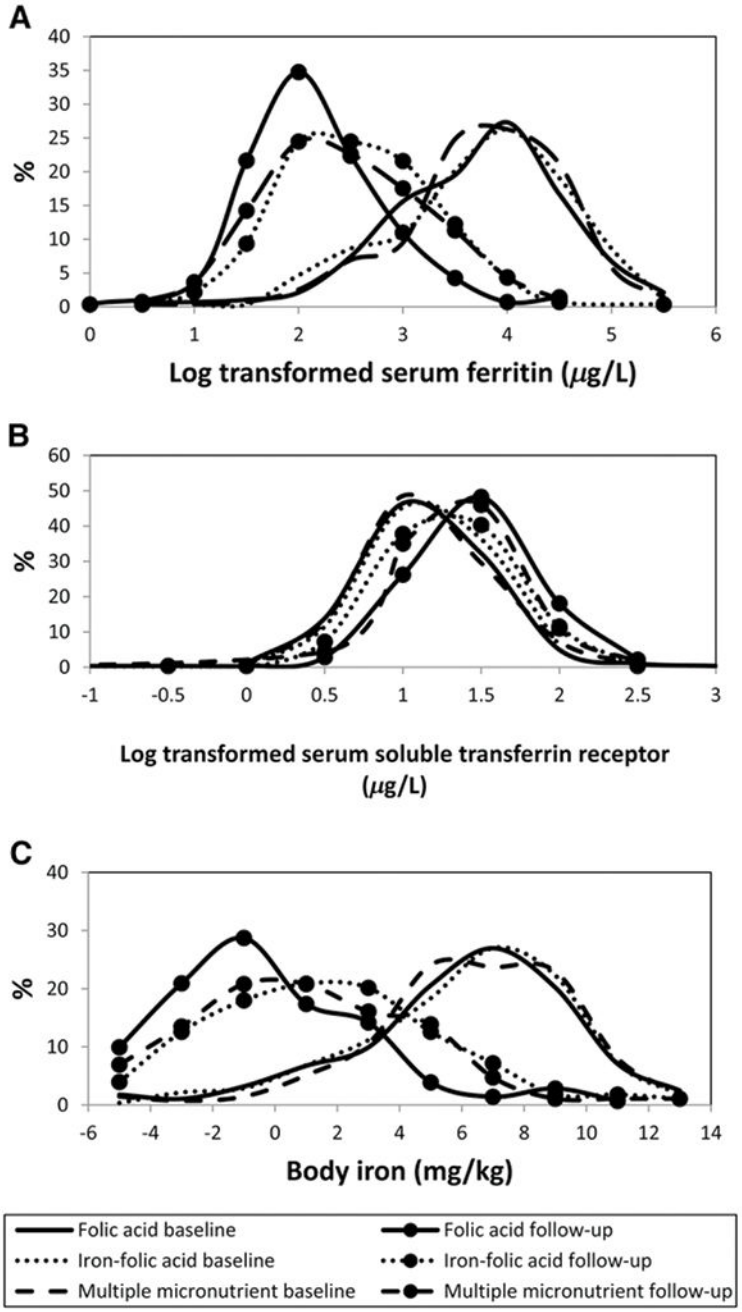

FIGURE 2.

Distributions of log-transformed serum ferritin (*A*), log-transformed serum soluble transferrin receptor (*B*), and body iron (*C*) calculated from serum ferritin and serum soluble transferrin receptor in Chinese pregnant women by intervention groups and timeline, from a randomized, double-blind trial in China, 2008–2010.

TABLE 1

Serum CRP and the prevalence of elevated CRP at baseline (4–19 wk gestational age) and follow-up (28–32 wk gestational age) by study group[1]

Group	*n*	Baseline	Follow-up	*P*[2]
CRP, *mg/L*				
Folic acid	282	1.53 (1.33, 1.77)	3.41 (3.04, 3.81)	<0.001
Iron–folic acid	278	1.60 (1.39, 1.86)	3.52 (3.15, 3.94)	<0.001
Multiple micronutrient	274	1.72 (1.49, 1.99)	3.36 (3.01, 3.77)	<0.001
CRP >5 mg/L, %				
Folic acid	282	17.7 (13.3, 22.2)	36.5 (30.9, 42.2)	<0.001
Iron–folic acid	278	18.7 (14.1, 23.3)	38.1 (32.4, 43.9)	<0.001
Multiple micronutrient	274	21.9 (17.0, 26.8)	33.9 (28.3, 39.6)	<0.001

[1] Values are geometric means (95% CIs) or percentages (95% CIs). At baseline, means or prevalence across groups were not significantly different ($P > 0.05$, 2-tailed *t* test). At follow-up, means or prevalence across groups were not significantly different after adjustment by baseline CRP amount, gestational age, and interaction term ($P > 0.05$, generalized linear model). CRP, C-reactive protein.

[2] Within each row, 2-tailed *t* tests were used for testing the means, and McNemar's test was used for the prevalence.

TABLE 2

Baseline maternal characteristics at enrollment by study group[1]

Characteristics	Folic acid (*n* = 282)	Iron–folic acid (*n* = 278)	Multiple micronutrient (*n* = 274)	*P*[2]
Maternal age, *y*	23.4 ± 2.5	23.1 ± 2.2	23.5 ± 2.5	0.13
Education				0.83
Primary or less	1.4	1.8	2.6	
Secondary	85.5	83.1	83.9	
High school or above	13.1	15.1	13.5	
Ethnicity				0.06
Han	96.1	98.6	98.9	
Other	3.9	1.4	1.1	
Occupation				0.33
Farmer	90.4	93.2	89.8	
Other	9.6	6.8	10.2	
BMI (kg/m^2)				0.87
<18.5	6.4	6.9	8.0	
18.5–24.9	74.8	74.8	75.2	
25.0–29.9	16.0	14.0	14.2	
≥30.0	2.8	4.3	2.6	
Height, *cm*	159.7 ± 4.8	160.4 ± 5.4	160.1 ± 4.9	0.32
Gestational week				0.43
<12	50.4	55.0	55.1	
≥12	49.6	45.0	44.9	
Hemoglobin (g/L)				0.10
100–109	5.3	7.2	3.3	
110–119	25.2	18.7	18.6	
120–129	39.0	45.7	47.1	
≥130	30.5	28.4	31.0	

[1] Values are means ± SDs or percentages.

[2] Chi-square tests were used to examine statistical differences in categorical variables and ANOVA was used to examine differences in means among study groups.

TABLE 3

SF, sTfR, BI, and hemoglobin at baseline (4–19 wk of gestation) and follow-up (28–32 wk of gestation) by study group[1]

Group	*n*	Baseline	Follow-up	*P*[2]
SF, *μg/L*				
Folic acid	282	51.4 (46.6, 56.8)	11.3 (10.4, 12.1)[b]	<0.001
Iron–folic acid	278	54.8 (49.8, 60.4)	16.7 (15.3, 18.1)[a]	<0.001
Multiple micronutrient	274	55.6 (50.7, 61.0)	15.0 (13.7, 16.5)[a]	<0.001
STfR, *μg/L*				
Folic acid	282	4.07 (3.88, 4.27)	4.79 (4.29, 5.34)[a]	0.006
Iron–folic acid	278	4.16 (3.97, 4.35)	3.99 (3.52, 4.53)[b]	0.547
Multiple micronutrient	274	4.06 (3.86, 4.27)	4.34 (3.84, 4.89)[a,b]	0.309
BI, *mg/kg*				
Folic acid	282	5.98 (5.55, 6.42)	−0.22 (−0.62, 0.17)[b]	<0.001
Iron–folic acid	278	6.15 (5.75, 6.54)	1.72 (1.29, 2.15)[a]	<0.001
Multiple micronutrient	274	6.28 (5.88, 6.67)	1.10 (0.65, 1.55)[a]	<0.001
Hemoglobin, *g/L*				
Folic acid	282	121.5 (120.5, 122.5)	124.5 (123.2, 125.7)[a]	<0.001
Iron–folic acid	278	121.5 (120.6, 122.5)	124.4 (123.2, 125.6)[a]	<0.001
Multiple micronutrient	274	122.4 (121.4, 123.4)	126.0 (124.8, 127.2)[a]	<0.001

[1] Data are geometric means (95% CIs) for SF and sTfR and arithmetic means (95% CIs) for BI and hemoglobin. Within each indicator at baseline, means across groups are not significantly different ($P > 0.05$, 2-tailed *t* test). Within each indicator at follow-up, means across groups with different superscript letters were significantly different (a > b, $P < 0.05$) after adjustment by group baseline amount of each indicator and gestational age and interaction term (generalized linear model). BI, body iron; SF, serum ferritin; sTfR, serum soluble transferrin receptor.

[2] Within each row, means between baseline and follow-up were tested by 2-tailed paired *t* test.

TABLE 4

SF, sTfR, BI, and hemoglobin at baseline (4–19 wk of gestation) and follow-up (28–32 wk of gestation) by study group[1]

Group	*n*	Baseline	Follow-up	*P*[2]
		% abnormal	*% abnormal*	
SF				
Folic acid	282	4.6 (2.2, 7.1)	59.6 (53.8, 65.3)[a]	<0.001
Iron–folic acid	278	5.4 (2.7, 8.1)	35.3 (29.6, 40.9)[b]	<0.001
Multiple micronutrient	274	3.7 (1.4, 5.9)	42.7 (36.8, 48.6)[b]	<0.001
sTfR				
Folic acid	282	40.4 (34.7, 46.2)	69.9 (64.5, 75.2)[a]	<0.001
Iron–folic acid	278	43.2 (37.3, 49.0)	53.6 (47.7, 59.5)[b]	0.008
Multiple micronutrient	274	39.8 (34.0, 45.6)	59.9 (54.0, 65.7)[b]	<0.001
BI				
Folic acid	282	6.0 (3.3, 8.8)	59.6 (53.9, 65.3)[a]	<0.001
Iron–folic acid	278	5.4 (2.7, 8.1)	34.5 (28.9, 40.1)[b]	<0.001
Multiple micronutrient	274	3.7 (1.4, 5.9)	41.2 (35.4, 47.1)[b]	<0.001
Hemoglobin				
Folic acid	284	6.9 (3.9, 9.8)	5.3 (2.7, 7.9)[a,b]	0.317
Iron–folic acid	278	6.2 (3.4, 9.1)	7.2 (4.2, 10.2)[a]	0.655
Multiple micronutrient	274	3.7 (1.5, 5.9)	3.3 (1.2, 5.4)[b]	0.782

[1] Data are percentages (95% CIs). Abnormal values for SF, sTfR, BI, and hemoglobin were <12 μg/L, >4.4 μg/L, <0 mg/kg, and <110 g/L, respectively. Within each indicator at baseline, percentages across groups are not significantly different ($P > 0.05$, χ^2 test). Within each indicator at follow-up, percentages across groups with different superscript letters were significantly different (a > b, $P < 0.05$) after adjustment by group baseline amount of each indicator and gestational age and interaction term (generalized estimating equations). BI, body iron; SF, serum ferritin; sTfR, serum soluble transferrin receptor.

[2] Within each row, percentages between baseline and follow-up were tested by McNemar's test.