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CLINICAL ARTICLE

A randomized controlled trial examining the addition of folic acid to iron supplementation in the treatment of postpartum anemia

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ABSTRACT

Objective: To evaluate the efficacy of adding folic acid to oral iron supplementation in postpartum women with anemia. *Methods:* A randomized controlled trial was conducted in the Netherlands between April 8, 2008, and August 31, 2010. A total of 112 postpartum women with anemia (hemoglobin <10.5 g/dL) were randomly allocated to receive 600 mg/day ferrous fumarate plus 1 mg/day folic acid (FFFA group) or 600/day ferrous fumarate alone (FF group) for 4 weeks. Primary outcome measures were hemoglobin and health status. Secondary outcome measures were fatigue, compliance, and adverse reactions. *Results:* No between-group differences were observed in hemoglobin and health status after treatment, and no differences were found in fatigue scores. Approximately 75% of all women reported having at least one symptom resulting from ferrous fumarate use. Constipation caused by ferrous fumarate was significantly associated with non-compliance ($P = 0.014$). *Conclusion:* The addition of folic acid to iron supplementation is not beneficial in women with postpartum anemia, as it has no effect on hematologic or health status parameters. Clinical Trial Registration: CCMO website NL21797.028.08 and Netherlands Trial Register NTR2232.

1. Introduction

Approximately 21% of women in high-income countries experience postpartum anemia, a condition characterized by tiredness, maternal infections, depression, and impairments in mother–child interactions and infant development [1–4]. Treatment of postpartum anemia could, therefore, contribute to maternal health and infant development. Health status is a multidimensional concept, which refers to self-perceived physical, mental, and social functioning, and can be assessed by standardized questionnaires [5].

For active erythropoiesis to take place, adequate supplies of folate, cobalamin (vitamin B12), and iron are needed [6]. A deficiency in any one of these can reduce erythrocyte production and, subsequently, the numbers of circulating erythrocytes; substantial reduction can result in anemia [6]. Folate and vitamin B12 are both required for the extensive DNA synthesis that accompanies the production of hundreds of billions of new erythrocytes each day [6]. A decrease in vitamin B12 concentration has been observed during pregnancy, but the concentration of the active moiety, holotranscobalamin, remains unchanged [7].

Pregnant women require supplementation with iron and folic acid because of the increase in maternal hematopoiesis, rapidly dividing cells in the fetus, and because of elevated urinary losses of these nutrients [8]. WHO recommends universal daily supplementation with 60 mg/day elemental iron and 400 μg/day folic acid for 6 months during pregnancy and for the first 3 months postpartum to prevent iron-deficiency anemia [9].

The management of postpartum anemia is unclear because of significant variations in treatment and outcome measures [10]. In a randomized controlled trial (RCT) [11], postpartum women with anemia treated with 80 mg/day ferrous iron, with or without 0.35 mg/day folic acid, were compared with placebo. Hematological parameters and subjective health conditions improved significantly in both treatment groups; however, no difference was found between women who did and did not receive folic acid [11]. All women were selected during their third trimester of pregnancy, when their hemoglobin levels were above 10 g/dL, and all started treatment after spontaneous delivery, without consideration of their hemoglobin level at that time. In

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addition, subjective health was determined without the use of a standardized health status questionnaire.

The aim of the present study was to determine whether the addition of folic acid to oral iron supplementation improved hemoglobin and health status in women with postpartum anemia. The effect of these agents on fatigue, compliance with treatment, and adverse reactions was also determined.

2. Materials and methods

The present RCT was conducted between April 8, 2008, and August 31, 2010, at the Department of Obstetrics and Gynecology, TweeSteden Hospital, Tilburg, in the southern part of the Netherlands. Approval was obtained from the local ethics committee (file number NL21797.028.08). All women received verbal and written information about the study, and provided verbal and written informed consent.

Women were eligible for inclusion if they were 18 years or older, thoroughly understood the Dutch language, and had indications for hemoglobin determination within 48 hours after delivery. Indications included estimated blood loss over 500 mL, delivery by cesarean, manual removal of the placenta, and clinical symptoms of anemia. Women were excluded for the following reasons: hemoglobin less than 6.4 g/dL (because the hospital protocol indicates the need for packed red cell transfusion); addiction to alcohol or drugs; hematological disease; vitamin B12 deficiency (serum vitamin B12 < 100 nmol/L and holotranscobalamin <20 pmol/L), methotrexate use; and contraindications for folic acid and ferrous fumarate.

Within 48 hours postpartum (T0), maternal venous blood was collected to determine hematological parameters, and health status was measured using the self-reported standardized 36-item Short-Form Health Survey (SF-36), the European Quality of Life questionnaire (EQ-5D), and the Visual Analogue Scale (VAS) of the EQ-5D. Fatigue was measured using the Checklist Individual Strength (CIS).

Anemia was defined, according to Dutch guidelines, as hemoglobin less than 10.5 g/dL [12]. Women were enrolled by random selection of opaque, taped envelopes containing a note reading "ferrous fumarate plus folic acid" (FFFA group) or "ferrous fumarate alone" (FF group). Doctors and the included women were not blinded to allocation as no placebo was used. All included women were prescribed 200 mg ferrous fumarate three times daily for 4 weeks, whereas women in the FFFA group were also prescribed 0.5 mg folic acid twice daily for 4 weeks. Women who did not have anemia (hemoglobin ≥10.5 g/dL) were excluded from randomization.

Women were followed up at the outpatient clinic 5 weeks after delivery (T5), at which time hematological parameters and health status were again measured. Compliance with medication was measured by counting the numbers of remaining tablets. Adverse effects were assessed using a list of symptoms that frequently occur after ferrous fumarate or folic acid use. This list was completed by the women themselves during the follow-up appointment.

Blood hemoglobin, erythrocyte mean corpuscular volume, erythrocyte volume fraction (hematocrit), erythrocyte mean corpuscular hemoglobin concentration, erythrocyte mean corpuscular hemoglobin, hemoglobin content in reticulocytes, and total reticulocyte count were analyzed using an Advia 2120i (Siemens Healthcare Diagnostics, Breda, Netherlands) automated cell counter. Total serum iron and total iron binding capacity (TIBC) were measured on an Advia 1650 chemistry analyzer (Siemens Healthcare Diagnostics). Transferrin concentration was measured on a Beckman Coulter Immage 800 immunochemistry analyzer (Beckman Coulter, Mijdrecht, Netherlands). Serum ferritin and folic acid were measured on an Advia Centaur immunoassay system (Siemens Healthcare Diagnositcs). Folic acid levels less than 7 nmol/L were considered indicative of folic acid deficiency.

Iron-deficiency anemia was defined as hemoglobin less than 10.5 g/dL plus mean corpuscular volume less than 80 fL or hemoglobin content in reticulocytes less than 28 pg (1.74 fmol) [13]. Hemoglobin, measured as mmol/L was converted to g/L by multiplying by 16.115, whereas hemoglobin measured as g/L was converted to mmol/L by multiplying by 0.062054. Iron saturation was calculated as (serum iron/ total iron binding capacity) x 100%.

The SF-36 is a generic questionnaire that was chosen because it covers all health status domains, and is often used in determining health status in postpartum women. Each of the 36 items has a scoring range from 0 to 100, with higher scores representing better levels of functioning [14]. In addition, the SF-36 provides a physical component summary, and a mental component summary.

The EQ-5D is a generic health status questionnaire containing five items, each with a scoring range from 1 to 3, with higher scores representing worse functioning [15]. Included in the EQ-5D is the VAS, which represents a global evaluation of health on a scale ranging from 0 (worst imaginable health status) to 100 (best imaginable health status). This questionnaire was chosen because of its simplicity and rapid completion time. Both the SF-36 and EQ-5D have demonstrated good psychometric properties in postpartum women [16].

The CIS is a multidimensional scale that quantifies subjective fatigue and related behavioral aspects [17]. This questionnaire was chosen because fatigue is a symptom of anemia. Each of the 20 items is scored from 1 to 7, with higher scores indicating greater fatigue. CIS is a reliable and valid tool in people with chronic fatigue syndrome, as well as in healthy populations [18].

The primary outcome measures were hemoglobin and health status increases after 4 weeks of treatment. Secondary outcome measures were fatigue, compliance, and adverse reactions.

Sample size calculation was based on the hypothesis that increases in hemoglobin concentration and health status over time would be greater in the FFFA than in the FF group. A-priori sample size calculation was carried out using analysis of variance for repeated measures by the G-power 3.1 calculator [19]. Assuming an effect size of 0.5, with an α-error of 0.05 and a power of 80%, a total sample size of 26 participants was required. To be able to undertake sub-analyses, the sample size was expanded to include 112 women with anemia.

All statistical analyses were conducted using SPSS 15.0 (IBM, Armonk, NY, USA). Baseline characteristics, compliance, and adverse effects in the two groups were assessed using independent sample *t* tests or χ^2 square tests. All analyses were conducted according to intention-to-treat principles. Analysis of variance for repeated measures was used to compare hematological parameters and health status scores in the two groups, with correction for the number of tests using the Bonferroni rule. All results are reported as mean ± standard deviation or percentage (%). $P < 0.05$ was considered statistically significant.

3. Results

The flow of participants through the study is shown in accordance with CONSORT criteria (Fig. 1). Of the 364 women screened, 53 did not meet the inclusion criteria, 42 were excluded owing to vitamin B12 deficiency, eight were excluded because hemoglobin was less than 6.4 g/dL, and three were excluded owing to language constraints. Eleven women declined to participate. Eighty women did not complete the baseline health status questionnaires for unknown reasons, and were therefore excluded, as were 108 women who did not have anemia (hemoglobin ≥10.5 g/dL). As a result, 112 women were randomly allocated between the groups. Of these, 91 women were available for analyses because 12 were lost to follow up, and nine withdrew. The demographic and clinical characteristics of the participants by treatment group are shown in Table 1. No relevant differences among the groups were detected at baseline. Each group included eight women with a serum folate deficiency at baseline ($P = 0.64$). Iron-deficiency anemia was present in 18 women in the FFFA group and 21 in the FF group (29% vs 42%, $P = 0.15$).

Intention-to-treat analyses showed no between-group differences in hematologic parameters, except for an expected significant difference

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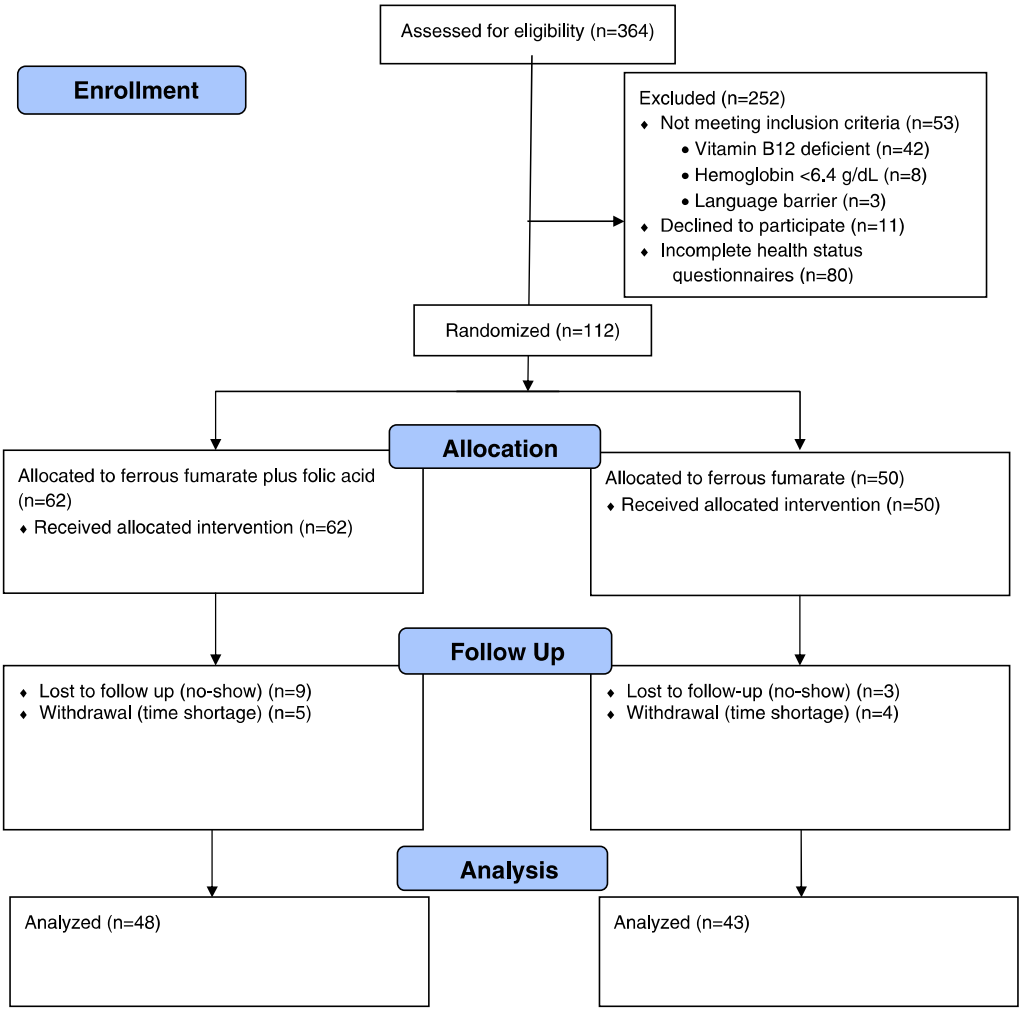

Fig. 1. Flow chart of patients.

Table 1
Patient demographic and clinical characteristics at baseline (T0).[a]

Characteristics	Ferrous fumarate plus folic acid (n = 62)	Ferrous fumarate (n = 50)
Age at entry, y	31.0 ± 4.7	30.1 ± 4.5
BMI before pregnancy	25.2 ± 4.7	25.3 ± 6.2
White	55 (88.7)	42 (84)
Highest education:		
Lower	3 (5.2)	3 (6.1)
Medium	29 (50)	27 (55.1)
High	26 (44.8)	19 (38.8)
Smoking	9 (14.5)	6 (12.2)
Multivitamin or folic acid use	30 (48.4)	18 (36)
Parity at baseline	1.6 ± 0.9	1.4 ± 0.7
Gestational age at delivery, wk	40.0 ± 1.6	40.0 ± 1.6
Delivery method:		
Vaginal	40 (64.5)	30 (60.0)
Cesarean	22 (35.5)	20 (40.0)
Estimated blood loss, mL	834 ± 436	811 ± 395
Infant feeding:		
Breastfeeding	36 (58.1)	34 (68)
Bottle (formula) feeding	26 (41.9)	16 (32)
Serum folate deficiency	8 (12.9)	8 (16)
Iron-deficiency anemia	18 (29.0)	21 (42.0)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters).
[a] Values are given as mean ± SD or number (percentage).

in serum folate concentration ($P = 0.001$) (Table 2). In addition, SF-36 and CIS scores were similar in the two groups (Table 3). The FFFA group reported higher pain scores on the EQ-5D ($P < 0.001$) and lower VAS scores ($P < 0.05$) compared with the FF group (Table 3).

At 5 weeks postpartum, 72.3% (n = 34) of the women in the FFFA group and 66.7% (n = 28) of those in the FF group reached non-anemic hemoglobin levels (>12.0 g/dL) ($P = 0.56$). When women in the two groups were stratified by baseline severe (hemoglobin 6.4–8.0 g/dL, n = 12) and moderate (hemoglobin 8.0–10.5 g/dL, n = 77) anemia, no significant between-group differences were found in the percentage of women with severe ($P = 0.68$) and moderate ($P = 0.93$) anemia attaining non-anemic hemoglobin levels (Fig. 2).

None of the women experienced serious adverse effects. However, 74.7% (n = 68) of all women, 77.1% in the FFFA (n = 37), and 72.1% in the FA group (n = 31) ($P = 0.58$) reported having at least one symptom as a result of ferrous fumarate use. The most common of these symptoms was colored feces and constipation, which were reported by 64.8% (n = 59) and 38.5% (n = 35) of these women, respectively. Only two women (4.3%) in the FFFA group reported skin rash as a result of folic acid use.

Of the women in both groups, 50.5% (n = 46) ingested all 84 prescribed ferrous fumarate tablets and 76.7% (n = 69) ingested more than 75% (>63 tablets). Of the women in the folic acid group, 62.5% (n = 30) ingested all 56 prescribed folic acid tablets, and 79.2% (n = 38) ingested

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Table 2
Hematology results at baseline (T0) and after 4 weeks of treatment (T5).[a]

	Ferrous fumarate plus folic acid		Ferrous fumarate	
	T0	T5	T0	T5
Hemoglobin, g/dL	9.2 ± 0.9	12.4 ± 1.0	9.2 ± 0.9	12.2 ± 1.1
Hematocrit,%	27 ± 3.0	38 ± 3.0	27 ± 3.0	37 ± 3.0
Mean corpuscular volume, fL	84.3 ± 5.4	85.4 ± 5.7	82.7 ± 6.1	83.9 ± 5.4
Mean corpuscular hemoglobin, fmol	1.76 ± 0.14	1.74 ± 0.14	1.73 ± 0.16	1.70 ± 0.13
Mean corpuscular hemoglobin concentration, mmol/L	20.9 ± 0.6	20.5 ± 0.7	21.0 ± 0.6	20.3 ± 0.7
Serum iron, μmol/L	11.7 ± 5.7	14.6 ± 8.0	12.2 ± 6.4	13.3 ± 10.4
Iron saturation, %	15.8 ± 8.1	22.8 ± 13.2	15.8 ± 8.7	20.9 ± 16.5
Total iron binding capacity, μmol/L	77.2 ± 14.8	64.9 ± 8.1	78.0 ± 11.1	66.3 ± 7.7
Ferritin, μg/L	32.1 ± 35.7	23.9 ± 9.0	22.5 ± 17.1	24.0 ± 12.3
Transferrin, g/L	3.7 ± 0.7	3.1 ± 0.4	3.7 ± 0.6	3.2 ± 0.5
Reticulocyte hemoglobin content, pg	1.87 ± 0.17	1.88 ± 0.18	1.86 ± 0.21	1.84 ± 0.18
Folic acid, nmol/L	15.3 ± 8.7	34.1 ± 13.3[b]	14.9 ± 11.1	19.4 ± 11.8[b]

[a] Values are given as mean ± SD.
[b] $P = 0.001$ by repeated measures of analysis of variance.

more than 75% (>42 tablets). Constipation caused by ferrous fumarate was associated with non-compliance. Women without constipation ingested 20 or more ferrous fumarate tablets than women with constipation ($P = 0.014$). No association was found between folic acid compliance and skin rash ($P = 0.28$).

4. Discussion

In the present RCT, the addition of folic acid to iron supplementation did not confer additional benefit, as shown by hemoglobin concentration and health status in women with postpartum anemia. Fatigue scores were also not affected by folic acid addition. Approximately 75% of the women in this trial reported having at least one symptom arising from ferrous fumarate use, with constipation caused by ferrous fumarate significantly associated with non-compliance.

An earlier RCT also found no difference in hematological parameters and subjective health conditions between postpartum women who did and did not receive folic acid, but probably also included women without postpartum anemia [11]. In contrast, an RCT in anemic pregnant women in Mexico found that hemoglobin levels were higher after iron and folic acid supplementation than after iron supplementation alone; those results were independent of serum folate concentrations [20]. The differences in diet and socioeconomic status between Mexican and European populations make it difficult to compare these findings with those of the present study.

Approximately 75% of all the women in this trial experienced an adverse effect of ferrous fumarate, which is higher than the 56% reported in a study involving pregnant women [21]. This difference may be attributable to the higher ferrous fumarate dose used in the present study, as adverse effects are dose related [22]. Iron dosage in the present study, however, was consistent with the recommended dosage of

Table 3
Health status by group at baseline (T0) and after 4 weeks of treatment (T5).[a]

Questionnaire	Ferrous fumarate plus folic acid		Ferrous fumarate	
	T0	T5	T0	T5
SF-36				
Physical functioning	39.8 ± 32.7	80.0 ± 18.7	43.4 ± 36.5	84.2 ± 16.2
Social functioning	64.3 ± 26.7	85.4 ± 19.2	71.5 ± 24.1	84.6 ± 23.3
Role physical	29.8 ± 38.9	64.9 ± 43.5	39.5 ± 38.3	74.4 ± 38.4
Role emotional	86.5 ± 33.8	87.2 ± 32.3	84.1 ± 31.4	96.0 ± 51.2
Mental health	78.4 ± 15.5	86.9 ± 11.3	79.5 ± 11.7	85.5 ± 11.0
Vitality	52.8 ± 22.2	65.5 ± 15.7	56.9 ± 18.4	66.8 ± 15.0
Bodily pain	56.0 ± 30.1	81.5 ± 20.4	65.0 ± 28.0	87.2 ± 19.4
General health	79.5 ± 15.3	79.7 ± 16.3	80.8 ± 11.6	80.3 ± 11.4
Health change	45.3 ± 21.0	45.8 ± 22.1	44.2 ± 14.3	47.1 ± 14.6
Physical component summary	50.8 ± 20.8	76.5 ± 20.2	57.6 ± 22.0	81.7 ± 17.2
Mental component summary	70.1 ± 18.5	81.5 ± 15.7	73.1 ± 14.5	84.0 ± 18.3
Total	58.8 ± 16.6	75.3 ± 15.2	63.2 ± 15.4	78.7 ± 15.1
EQ-5D				
Mobility	1.96 ± 0.71	1.17 ± 0.38	2.02 ± 0.77	1.07 ± 0.26
Self care	1.69 ± 0.62	1.04 ± 0.20	1.77 ± 0.72	1.00 ± 0.00
Daily activities	2.21 ± 0.68	1.38 ± 0.57	2.16 ± 0.81	1.28 ± 0.50
Pain and discomfort	1.94 ± 0.38	1.52 ± 0.55[b]	1.70 ± 0.51	1.23 ± 0.43[b]
Anxiety and depression	1.17 ± 0.38	1.13 ± 0.33	1.16 ± 0.37	1.09 ± 0.29
Total	8.94 ± 2.05	6.23 ± 1.49	8.81 ± 2.49	5.67 ± 0.99
Visual analogue scale	65.7 ± 16.2	76.9 ± 12.4[c]	71.1 ± 13.2	81.8 ± 9.3[c]
Checklist individual strength				
Subjective fatigue	36.9 ± 12.4	26.6 ± 11.5	33.3 ± 12.4	25.8 ± 10.0
Reduced motivation	13.1 ± 6.1	8.1 ± 3.3	13.1 ± 5.4	9.2 ± 4.0
Reduced activity	12.2 ± 5.6	7.8 ± 4.4	11.4 ± 5.5	8.4 ± 3.6
Reduced concentration	15.8 ± 8.1	13.2 ± 8.0	14.4 ± 6.9	13.6 ± 7.3
Total	77.7 ± 27.5	55.8 ± 21.8	71.6 ± 25.0	57.1 ± 18.7

[a] Values are given as mean ± SD.
[b] $P < 0.001$.
[c] $P < 0.05$ by repeated measures of analysis of variance.

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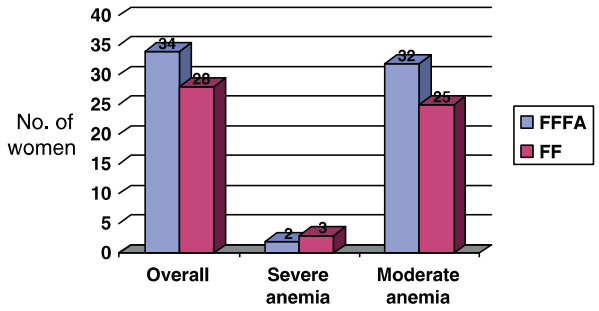

Fig. 2. Number of women per group with hemoglobin over 12.0 g/dL at 5 weeks postpartum. FF = 600 mg per day ferrous fumarate alone for 4 weeks; FFFA = 600 mg/day ferrous fumarate plus 1 mg/day folic acid.

100–200 mg/day ferrous iron in women with slight-to-moderate postpartum anemia [23]. Non-compliance owing to gastrointestinal adverse effects is consistent with previous findings [22].

Although the study participants were randomized between the two treatment arms, the results of randomization were not blinded, and therefore may have influenced study outcomes. Serum folic acid concentration, however, increased significantly over time in the FFFA group compared with the FF group, suggesting that the lack of placebo did not alter the results substantially. Although central randomization is generally recommended, participants in the present study were randomized using concealed opaque envelopes. There is no evidence, however, that the use of these envelopes differed from central randomization [24]. Hematology outcomes were only measured up to 5 weeks after delivery. These outcomes may have been different after a longer follow-up period. As erythroblast maturation takes 5–7 days, however, any between-group difference in hemoglobin concentrations would have been detected after 5 weeks [25].

Because this study included women of different ages, educational levels, parity, and modes of delivery, the results are applicable in daily medical practice. The addition of folic acid to iron supplementation does not benefit women with postpartum anemia, and is not required in daily practice in high-income countries. The present study was conducted in the Netherlands, and most women were white with western dietary habits; therefore, these results cannot be extrapolated to low-income countries.

In conclusion, the addition of folic acid to iron supplementation does not improve hemoglobin, health status, and fatigue in women with postpartum anemia. Oral iron supplementation was associated with a high rate of adverse effects, such as constipation. Constipation was significantly associated with non-compliance.

Conflict of interest

No conflict of interest.

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