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A randomized trial investigating an iron-rich natural mineral water as a prophylaxis against iron deficiency in pregnancy

D. McKENNA*, D. SPENCE*, S.E. HAGGAN*, E. MCCRUM*, J.C. DORNAN*, T.R. LAPPIN†

**Royal Victoria Hospital, Belfast, Northern Ireland, UK.*
†Belfast City Hospital, Belfast, Northern Ireland, UK.

Summary Spatone Iron-Plus is a naturally occurring mineral water from Trefriw Wells Spa in Conwy County, North Wales, UK. It contains approximately 0.20 mg of iron per millilitre as ferrous sulphate and has been shown to provide iron in a highly bio-available form. A 24 ml sachet contains approximately 5 mg of iron. Iron deficiency is common in the obstetric population. However, compliance with traditional iron supplements is poor because of gastrointestinal side-effects. We designed a randomized, double-blind, placebo-controlled trial. A total of 102 low-risk antenatal patients, who were noncompliant with routinely prescribed ferrous sulphate tablets, were randomized to receive 48 ml of Spatone water or placebo. The study was conducted between 22 and 28 weeks gestation. Primary outcome measures were compliance, gastrointestinal side-effects and changes in ferritin levels during the trial period. Compliance in the intervention group was 57% compared with 67% in the control group, $P = 0.22$. Dyspepsia scores, as determined by a recognized and well-validated questionnaire, did not differ between the two groups. During the trial period, mean ferritin levels fell by 24% in the Spatone Iron-Plus group compared with a mean fall of 51% in ferritin levels among the control group, $P = 0.016$.

Keywords pregnancy, iron deficiency, natural iron source, prophylaxis

Introduction

Iron-deficiency anaemia is common in the obstetric population (Mayet, 1985). The WHO (World Health Organisation) defines anaemia in pregnancy as a haemoglobin level <11.0 g/dl (WHO, 1972). In the development of iron deficiency, a low serum ferritin is the first abnormal laboratory test. Serum ferritin accurately reflects iron stores and the normal range in healthy adult females is 15–300 μg/l (Jacobs *et al.*, 1972). A level of 12 μg/l or below is indicative of iron deficiency. One study has shown that iron deficiency (serum ferritin <12 μg/l) is present in 35% of pregnant women in the first trimester, rising to 86% in the third trimester (Mayet, 1985). Anaemia in pregnancy is of particular concern at the time of delivery. The average volume of blood lost by a mother during an uncomplicated normal vaginal delivery is slightly more than 500 ml, whilst vaginal delivery of twins or uncomplicated caesarean sections is associated with a loss of nearly 1000 ml (Pritchard *et al.*, 1962; Deleeuw *et al.*, 1968; Euland, 1976).

There is no agreement among obstetricians about the desirability of giving prophylactic iron supplements to all antenatal patients (Hibbard & Horn, 1988). The physiological requirements for iron in pregnancy exceed the usual intake of most healthy women with good diets. Vegetarians are at particular risk. A large proportion of women who do not take iron supplements in pregnancy have no measurable iron stores at delivery (Fenton, Cavill & Fisher, 1977). A further argument for routine iron supplementation is that children of non-anaemic women who have not received supplements have lower iron stores than those of iron-supplemented women (Fenton *et al.*, 1977). However, there

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Correspondence: Dr Daniel McKenna, 88A, Malone Road, Belfast, BT9 5HP, Ireland, UK. Tel.: 028 92665141; Fax: 028 92634965; E-mail: dan.mckenna@virgin.net

was concern that iron supplements may interfere with zinc metabolism and maternal zinc levels during pregnancy (Hambridge *et al.*, 1983; Meadows *et al.*, 1983). These fears were compounded by reports suggesting that maternal zinc depletion was associated with intrauterine foetal growth restriction (Meadows *et al.*, 1981). Further study has shown that zinc levels fall physiologically during pregnancy and that iron supplements do not have any effect on maternal zinc levels (Sheldon *et al.*, 1985). On balance, the argument for routine iron supplements to all pregnant women would appear to be greater, especially as there is no evidence of harm. Compliance with iron supplements however, is often poor, mainly because of the gastrointestinal side-effects. In one study, 28% of patients reported side-effects of oral iron, leading to 10% of patients stopping their medication (Hallberg, Ryttinger & Solvell, 1966). Prophylactic treatment is usually given in the form of ferrous sulphate at a dose of 200 mg once or twice daily. In this form, 200 mg of ferrous sulphate contains 65 mg of elemental iron. At best, only 10% of iron in this form will be absorbed. Absorption of iron is greatest in the anaemic patient and, in the nonanaemic patient, a maximum daily absorption of 2.0 mg of iron would be expected (Finch & Cook, 1984).

Spatone Iron-Plus is a naturally occurring mineral water from Trefriw Wells Spa in Conwy County, North Wales, UK. It contains approximately 0.20 mg of iron per millilitre as ferrous sulphate. A study in a nonpregnant population has shown that Spatone Iron-Plus provides iron in a highly bioavailable form (Worwood *et al.*, 1996). We designed a randomized, double-blind, placebo-controlled trial to assess the use of Spatone Iron-Plus as a prophylaxis against iron deficiency in pregnancy.

Materials and methods

Protocol

The local Ethics Committee approved the study. Patients were recruited from the antenatal clinics at the Royal Jubilee Maternity Hospital, Belfast. In this hospital, all antenatal patients are routinely prescribed 200 mg of ferrous sulphate at their booking visit, to be taken from 18 weeks gestation until term. Recruits to this study were patients who were non-compliant with this regimen. The inclusion criteria for the study were patients with a singleton pregnancy; booking haemoglobin >10.4 g/dl and known gestational age confirmed by ultrasound at <20 weeks gestation. The exclusion criteria were patients with multiple pregnancy; booking haemoglobin <10.4 g/dl; uncertain gestational age; known medical problem; maternal ingestion of other medication; patients compliant with prescribed iron supplements and known foetal anomaly.

Assessment of patients coincided with routine antenatal visits to the hospital, at 22 and 28 weeks gestation. At 22 weeks gestation, a blood sample (10 ml) was taken for ferritin, haemoglobin and reticulocyte count. The routine haematological investigations were performed using a Sysmex Model SE 9500 and the reticulocyte counts were performed on a Sysmex R3500 utilizing the Auramine O Method (Sysmex UK Ltd, Milton Keynes, UK).

At this time, baseline gastrointestinal symptoms were assessed and recorded using the mGDSS (El-Omar *et al.*, 1996). It is a well-validated and easy-to-use questionnaire. Dyspepsia is a term that encompasses a combination of symptoms including epigastric pain, bloating, indigestion, fullness, nausea and vomiting (Heatley & Rathbone, 1987). These are all symptoms reported by patients on iron supplements and we modified the Glasgow Dyspepsia Severity Score (GDSS) by also including the symptom of constipation. Ferritin, haemoglobin and reticulocytes were checked at the end of the study, at 28 weeks gestation. The GDSS was assessed 4 weeks into the trial by telephoning the patient. The assessor and patient were blinded to the content of the sachets.

Primary outcome measures were compliance with treatments during the trial period; the modified Glasgow Dyspepsia Severity Scores (mGDSSs) and ferritin levels at trial entry at 22 weeks gestation; the mGDSSs at 26 weeks gestation and ferritin levels at the end of the study, at 28 weeks gestation. Secondary outcome measures were reticulocyte counts and haemoglobin levels at 22 and 28 weeks gestation.

Statistical analysis was performed using SPSS (SPSS Inc., 1999). Categorical variables were compared between the two groups using the chi-squared test and continuous variables compared using the independent sample *t*-test. Paired *t*-tests were used to compare mean values between 22 and 28 weeks gestation.

Assignment

Patient allocation was computer-generated before commencement of the trial by a medical statistician in the Department of Epidemiology and Public Health at Queen's University, Belfast. Randomization was restricted to achieve balance. This was sent to Trefriw Wells Spa in Conwy County, North Wales, UK. Here, 24 ml sachets of Spatone Iron-Plus (Spatone Ltd, Trefriw, UK) or placebo were made up according to the randomization sheet received from the statistician. The sachets for each subject

were placed in numbered bags, the bags being numbered 1–101. The randomization code stayed with the manufacturers until the end of the trial. There was no need to break the code during the trial. After suitability for the trial was ascertained and written consent obtained, patients were allocated their treatment consecutively, starting with bag number 1–101. The first two authors of the paper performed recruitment, consent and data collection. Patients were instructed to take two sachets daily, half an hour before breakfast. They were advised to expect a metallic taste from the contents of the sachets and were instructed to dilute the sachets in cordial orange juice. The iron content of the sachets was analysed independently by: City Analytical Services PLC of Coventry, UK. The 24 ml sachets of Spatone water contained an average iron content of 0.21 mg/ml.

Masking

The sachets for both the intervention and control groups were made from opaque silver foil. The placebo sachets contained deionized water adjusted to pH 2.9 (the pH of the spa water) with sulphuric acid.

Results

A total of 285 patients were considered for entry to the trial; 183 were excluded; and 130 patients were compliant with ferrous sulphate as prescribed, for prophylaxis; twenty patients were not taking iron supplements but declined to enter the trial; eleven patients had a known medical problem; nine booked late in their pregnancy; five had a booking haemoglobin <10.4 g/dl; five were carrying twin pregnancies and three had a known foetal abnormality. The two groups were comparable with regards to baseline maternal characteristics (Table 1).

Compliance in the intervention group was 29 of 51 (57%) compared with 35 of 51 (67%) in the control group, $P = 0.22$. There was no statistical difference in the mGDSS between the intervention and control groups (Tables 2 and 3). In the intervention (Spatone Iron-Plus) group, six of 29 (21%) had a higher mGDSS 4 weeks into the trial compared with three of 35 (9%) in the control group, $P = 0.17$. There was a fall in ferritin levels in both groups during the trial period (Table 2). Mean ferritin levels fell by 24% in the intervention group compared with a mean fall of 51% in ferritin levels among the control group, $P = 0.016$. In the intervention group nine of 29 (31%) of patients raised their ferritin levels during the trial period compared with four of 35(11%) in the control group, Relative Risk (RR) 2.72 (0.93, 7.92), $P = 0.05$.

Table 1. Baseline characteristics

	Spatone $n = 51$	Placebo $n = 51$	P
Age (mean)	28.6	25.9	0.02*
Married (%)	60.8	45.1	0.11
Parity 2+ (%)	23.5	25.5	0.69
Alcohol (%)	33.3	35.3	0.84
Cigarettes (%)	25.5	41.2	0.09
Booking weight (kg) (mean)	66.1	66.1	0.99

*excluding dropouts age $P = 0.28$.

Discussion

Iron supplements are regularly given in pregnancy to both anaemic and non-anaemic patients. In our unit, they are prescribed to all patients from 18 weeks gestation. Of those considered for entry into the trial, only 54% (154 of 285) were complying with this treatment at 22 weeks gestation. This may be due to the perceived noxious side-effects of iron supplements or it may be indicative of how effective we are in educating our pregnant population with regard to their health in pregnancy.

We recruited 102 of these noncompliant patients into our trial. Overall compliance during the trial period was 63% (64 of 102). In the development of the GDSS, the investigators found that nondyspeptic controls have a mean score of 1.16 (range 0–7; El-Omar *et al.*, 1996). In the first trimester, nausea is a common symptom and heartburn is common in the third trimester as a result of the gravid uterus exerting upward pressure on the stomach and lower oesophagus. In our population, mean dyspepsia scores did not change after 4 weeks treatment in either group. Gastrointestinal side-effects as a result of iron supplements in pregnancy are dose-related (Hallberg *et al.*, 1966). In nonanaemic patients, 2 mg of iron will be maximally absorbed daily. Two hundred milligrams of ferrous sulphate contains 65 mg of elemental iron. Only a small proportion of this will therefore be absorbed, increasing the likelihood of gastrointestinal side-effects. Spatone water contains 0.21 mg of iron/ml, minimizing the likelihood of gastrointestinal side-effects. One 24 ml sachet of Spatone water contains approximately 5 mg of iron. This small amount of iron ensures minimal upper gastrointestinal upset. Furthermore, as the majority of this iron is absorbed (Worwood *et al.*, 1996), only small amounts reach the colon, minimizing the risk of constipation.

Serum ferritin levels are not routinely checked in antenatal clinics. Haemoglobin levels are routinely checked and iron supplements offered on the basis of

Table 2. Mean values at 22 and 28 weeks gestation

	Spatone ($n = 29$)			Placebo ($n = 35$)		
	22 weeks gestation	28 weeks gestation	P	22 weeks gestation	28 weeks gestation	P
mGDSS	3.54 (3.48)	3.51 (3.38)*	0.92	1.86 (2.06)	1.54 (1.95)*	0.10
Hb	11.7 (1.1)	11.2 (1.1)	<0.01	11.4 (0.90)	11.0 (1.0)	<0.01
Retic	1.55 (0.49)	1.44 (0.46)	0.11	1.60 (0.41)	1.42 (0.30)	<0.01
Ferritin	17.7 (10.2)	13.4 (10.2)	0.01	21.2 (15.5)	10.4 (6.2)	<0.0001

*26 weeks (values given are mean ± 2SD).

Table 3. Difference between 22 and 28 weeks gestation

	Spatone ($n = 29$)	Placebo ($n = 35$)	P
mGDSS*	0.029 (1.60)	0.32 (1.18)	0.37
Hb	0.53 (0.89)	0.35 (0.64)	0.37
Retic	0.11 (0.35)	0.18 (0.33)	0.40
Ferritin	4.26 (8.65)	10.88 (12.02)	0.02

*Between 22 and 26 weeks gestation.
Values given are mean (±2SD); Hb (g/dl), Ferritin (μg/l), Retic (% red cells).

haemoglobin levels. However, haemoglobin levels do not accurately reflect iron stores. During pregnancy, haemoglobin levels do not significantly change, from 10–14 weeks until term. This is true for both patients taking supplements and those not taking supplements (Fenton *et al.*, 1977). Serum ferritin levels fall in both iron-supplemented and non-iron-supplemented patients until 28 weeks gestation. However, iron supplements maintain ferritin levels above what would be considered iron deficiency levels (<12 μg/l). After 28 weeks gestation, serum ferritin levels rise in patients taking iron supplements (Fenton *et al.*, 1977). This coincides with the time patients are most at risk for developing problems with iron deficiency, around the time of delivery. An emergency iron balance of 250 mg is required for a 500 ml bleed and 500 mg of iron is required for a 1 l bleed. Logic would suggest that iron stores should be boosted with supplements, in anticipation of delivery. In those patients randomized to Spatone Iron-Plus, the mean ferritin level at the end of the trial was 13.4 μg/l. In patients randomized to placebo, the mean ferritin level was 10.4 μg/l at 28 weeks gestation. These results contrast with mean ferritin levels among the Spatone Iron-Plus and placebo groups at trial entry of 17.7 and 21.2 μg/l, respectively. Spatone Iron-Plus ensures ferritin levels do not fall as precipitously as placebo during the period of 22–28 weeks gestation, $P = 0.02$. The trial ended at 28 weeks gestation, but we hypothesize that ferritin levels, and thus iron stores, may have risen if treatment had been continued until term.

In conclusion, iron deficiency is common in late pregnancy and is a potential cause of both maternal and foetal morbidity. The traditional method of screening patients for iron deficiency by measuring their haemoglobin level is neither sensitive nor specific. Patient compliance with traditional iron supplements is poor and a large number of patients stop their supplements because of gastrointestinal side-effects. In this paper, we have shown that Spatone Iron-Plus does not cause these side-effects and helps to prevent iron deficiency in pregnancy. It should be considered for use as a prophylaxis against iron deficiency in pregnancy. A randomized trial comparing it with traditional iron supplements would be worthwhile.

Trial profile

Total population considered ($n = 285$)

Patients excluded ($n = 183$)

Randomized ($n = 102$)

Spatone ($n = 51$)	Placebo ($n = 51$)
Number not reaching primary endpiont ($n = 22$)	Number not reaching primary endpoint ($n = 16$)
Stopped (no reason) $n = 11$	Stopped (no reason) $n = 8$
Nausea $n = 4$	Bad taste $n = 3$
Bad taste $n = 3$	Nausea $n = 2$
No 28-week blood sample $n = 3$	No 28-week blood sample $n = 2$
Constipation $n = 1$	Hb <10.4 g/dl at trial entry $n = 1$
Number analysed for Primary end-point ($n = 29$)	Number analysed for Primary end-point ($n = 35$)

Glasgow Dyspepsia Severity Score

(A) Over the past 4 weeks how frequently have you experienced dyspeptic symptoms?
Please tick one box

Never

On only 1 or 2 days

On approx. 1 day/week

On approx. 7 or 8 days

On approx. 50% of days

(B) Does the dyspepsia interfere with normal activities such as eating, sleeping or socializing?

Never

Sometimes

Regularly

(C) How many days have you lost off work due to your dyspepsia in the past 4 weeks?

None

1–7 days

More than 7 days

(D) How often have you attended a doctor due to dyspepsia in the past 4 weeks?

None

Once

Twice or more

(E) How often have you called your GP to visit you at home because of your dyspepsia in the past 4 weeks?

None

Once

Twice or more

(F) How many tests have you had done for your dyspepsia in the past 4 weeks?

None

One

Two or more

(G) Over the last 4 weeks, how frequently have you used drugs which you have obtained by yourself?

Never

Less than once per week

More than once per week

Name of drug

1. 2.

3. 4.

(H) Over the last 4 weeks, for how long have you used drugs prescribed by a doctor?

Never

For 1 week or less

For 1–3 weeks

For more than 3 weeks

Name of drug

1. 2.

3. 4. Total Dyspepsia Score:

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