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Iron absorption from Spatone (a natural mineral water) for prevention of iron deficiency in pregnancy

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Summary

The absorption of iron from Spatone Iron-Plus has been investigated in pregnant women with iron deficiency anaemia. A total of 25 mg Fe was taken and absorption determined from the increase in serum iron concentration during a period of 3 h. Mean absorption was 28%, significantly higher than in nonpregnant, nonanaemic women (14%). These studies demonstrate that Spatone provides an alternative to the standard ferrous sulphate tablet for prevention of iron deficiency in pregnancy. As only lower doses of iron are required, the unpleasant side-effects of iron therapy are largely avoided.

Keywords

Iron absorption, iron deficiency, pregnancy, supplementation

Introduction

Most of the 3–4 g iron in the human body is found in haemoglobin, the oxygen carrying pigment of the red blood cell. There are smaller amounts in myoglobin, in muscle and even less in the multitude of iron containing proteins responsible for oxygen utilization in all cells. A variable amount of 'storage iron' is found in the tissues as ferritin and haemosiderin. For a review of iron metabolism see Sherwood *et al.* (1998). In men, iron losses are limited to about 1 mg Fe/day, regardless of the amount of iron in the body. Menstruation increases daily iron losses in women to 1.4 mg and the net loss of iron in pregnancy corresponds to a mean daily loss of nearly 3 mg/day (British Nutrition Foundation, 1995). Infants are born with high levels of haemoglobin and storage iron but after 6 months of age iron requirements are high, relative to body weight because of the demand for iron caused by rapid growth. The iron content of the body is regulated by variation in the amount of iron absorbed from the diet. Western diets usually contain about 10–15 mg Fe and about 10% is retained in the body. This level of intake is usually adequate for men but – although iron absorption

percentage increases with decreasing levels of storage iron – women and children must generally obtain larger amounts of iron from a smaller dietary intake.

Iron deficiency, defined as an absence of storage iron, is therefore relatively common in children and women of childbearing age. The level of storage iron may be estimated by measuring the serum ferritin concentration. Concentrations of <15 µg/l indicate the absence of storage iron and a value of 300 µg/l is equivalent to iron stores of about 2 g (the maximum normally found). Hallberg *et al.* (1993) considered that the best indicator of iron deficiency was a ferritin concentration of <16 µg/l, and have concluded that approximately 30% of young women in Europe and North America are iron deficient. However, improving specificity by the application of multiple measures (i.e. a low serum ferritin and a low transferrin saturation) suggested that approximately 12% of young women in North America may be iron deficient (Cook *et al.*, 2001). If iron losses continue, iron deficiency anaemia will develop (Baynes, 1994). Iron deficiency anaemia causes tiredness and breathlessness, and is associated with other physical and behavioural abnormalities, particularly in childhood. In North America and Europe the incidence of iron deficiency anaemia in women is about 10% and in parts of the developing world the incidence is over 50% (DeMaeyer *et al.*, 1985).

Iron deficiency anaemia is the most common haematological problem in pregnancy. In some hospitals prophylactic iron is given to all women during pregnancy but

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there is no agreement about the desirability of this practice and in other hospitals iron is only prescribed when anaemia develops (Hibbard, 1988; Horn, 1988). Iron must be added to infant formulas and follow-on formulas (except those used only during the first 4 months of life) to meet the composition given in the European Community Directive 91/321/EEC. In the UK, white flour is supplemented to increase the iron content to that of wholemeal flour (Department of Health and Social Security, 1981). This iron is poorly available and there is little evidence about its efficacy (Department of Health and Social Security, 1981). Universal fortification of food may have undesirable consequences for the one in 200 people in Northern European populations with genetic haemochromatosis, a disorder in which too much iron is absorbed (Olsson *et al.*, 1997). However, the prevalence of clinical haemochromatosis is much lower than this (McCune *et al.*, 2002) and the significance of fortification for increasing morbidity because of iron overload is not known.

Tonics and food supplements containing iron are widely available and have been used for centuries. Such supplements should ideally contain iron that is highly available, should not cause side-effects and should not be absorbed by those with high levels of storage iron who do not need additional iron. Spatone Iron-Plus is a naturally occurring spa water from Trefriw Wells in Gwynedd (Wales), which contains approximately 0.21 mg of iron/ml as ferrous sulphate in solution. The water has been taken as a tonic since Victorian times. Iron absorption from Spatone Iron-Plus was measured in a whole body counter after labelling the Spatone with ^{59}Fe ferrous sulphate. Absorption studies were carried out in 13 subjects. Mean absorption from 3 mg Spatone Iron-Plus taken in empty stomach was 23%. Absorption was related to body iron stores as assessed by serum ferritin. In subjects with a serum ferritin concentration of $<10\ \mu\text{g/l}$, absorption was approximately 40% but was $<10\%$ in subjects with ferritin concentrations of approximately $200\ \mu\text{g/l}$. This study indicated that Spatone Iron-Plus provides iron in a highly bio-available form (Worwood *et al.*, 1996).

The aim of the present study was to measure the absorption of iron from Spatone in pregnant, anaemic subjects and to assess its potential value in preventing iron deficiency anaemia.

Subjects and methods

The serum iron response to Spatone was measured in 12 women in the third trimester of pregnancy with iron deficiency anaemia (Hb $<10.5\ \text{g/dl}$ and serum ferritin

$<15\ \mu\text{g/l}$). There is some variation in serum iron concentration with time in the absence of food or iron intake and this was assessed in six pregnant women (third trimester) with iron deficiency anaemia (Hb $<10.5\ \text{g/dl}$ and serum ferritin $<15\ \mu\text{g/l}$) who took deionized water. In order to compare the serum iron response with that in women with normal iron stores who were not anaemic, Spatone was administered to 15 women aged 20–45 years who were neither pregnant nor anaemic, and deionized water to another nine women. These women were volunteers from the staff at the Royal Glamorgan Hospital with Hb $>11.5\ \text{g/dl}$ and serum ferritin $>15\ \mu\text{g/l}$.

The study protocol was approved by the Ethics Committee of Bro Taf Health Authority. Potentially pregnant and anaemic participants were identified from notes and consultation with the respective clinicians. They were given oral and written information and gave informed consent. All subjects fasted from midnight on the day before the test. They were allowed to drink water but not tea or coffee (which impair iron absorption) or juice drinks which may enhance iron absorption. Each participant received a payment of £40 to compensate for the time and inconvenience of the study.

At the outset, the women were weighed and a baseline venous blood sample was drawn to obtain a blood count and measure serum iron concentration, total iron binding capacity (TIBC) and serum ferritin prior to the administration of the fluid.

Either the contents of sachets of Spatone (120 ml containing 25 mg Fe) or the sachets of deionized water (120 ml at the same pH of 2.9) were taken. Up to 100 ml of deionized water could be taken afterwards if required, to cleanse the palate. Spatone provided both the product and deionized water packed in sachets under nitrogen to prevent oxidation of iron. This is the usual market formulation. These sachets had random numbers attached at the University of Glamorgan (LM). Subjects were also allocated one of the random numbers. Participants and samples were paired and the sample identified at the end of the study (i.e. it was double-blind).

Further venous blood samples (5 ml, clotted) were taken by a midwife (GH) at 30 min, 1, 2 and 3 h using a butterfly needle. Subjects remained seated or lying down during the study as far as possible. During this time they did not drink tea or coffee, but were allowed to drink water *ad libitum* an hour after the initial sample was taken.

Dextrose and additional food were available if anyone felt faint. Withdrawal from the study might occur at any time if the participant so wished, or if there were clinical indications for doing so. Food was provided for every participant after the last blood sample was taken.

Blood was collected in labelled, serum sample bottles with clot retractant. The bottles were collected daily and transported to the Haematology Department at the University of Wales College of Medicine. Serum iron concentration and TIBC were measured (Worwood, 2001), and serum ferritin by immunoassay (Elecsys 2010 system; Roche Diagnostics, Lewis, UK). Percentage iron absorption was calculated from the maximum increase in serum iron concentration as described by Ekenved *et al.* (1976). The maximum value occurred 2 or 3 h after taking Spatone. The mean change in serum iron concentration between 0 and 3 h for women taking water was subtracted from the increments after Spatone for each group.

The data were entered into an electronic format at the College of Medicine, and at the end of the data collection period were supplied to the University of Glamorgan. The samples were decoded and the analysis completed.

Results

Mean values for body weight, serum iron, transferrin saturation and serum ferritin concentration are shown in Table 1. Mean body weight did not differ for the pregnant and nonpregnant women but the anaemic women had low serum iron, transferrin saturation and serum ferritin concentrations compared with the nonpregnant women. Changes in serum iron concentration in women taking Spatone or water are illustrated in Figure 1. The mean increment in serum iron concentration for nonpregnant women taking water was 1.4 $\mu\text{mol/l}$ and for those taking Spatone was 11.7 $\mu\text{mol/l}$. For pregnant, anaemic women the increment was 0.6 mol/l for those taking water and 15.3 $\mu\text{mol/l}$ for those taking Spatone. Before allowing for blood volume changes in pregnancy, the percentage iron absorption was 13.8% in the nonpregnant women and 19.6% in the anaemic, pregnant women ($P = 0.042$, two sample *t*-test). After correction for the increase in plasma

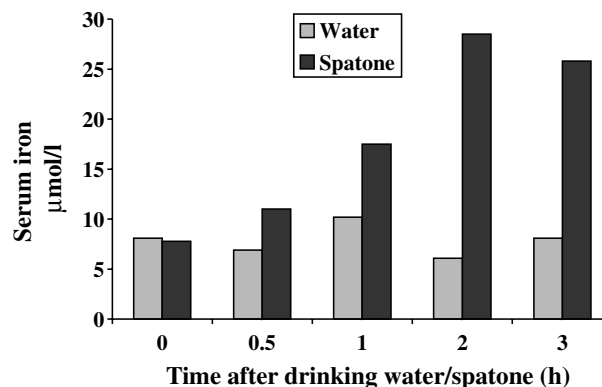


Figure 1. Change in serum iron concentration with time (the response in pregnant, anaemic women, one drinking deionized water and one Spatone).

volume (a factor of 1.44 for late pregnancy; Lange & Dynesius, 1972) absorption was 28.2% in pregnant women significantly higher than in nonpregnant women ($P < 0.001$, two sample *t*-test).

There was no relationship between percentage iron absorption and weight in either group of women. Furthermore, there was no relationship between iron absorption and transferrin saturation or serum ferritin concentration in either group. This was because groups were selected to be anaemic or nonanaemic. Numbers were small and there was relatively little variation in iron status within each group.

Discussion

Pregnancy leads to a mean loss of about 680 mg Fe. This is because of the following iron needs: 170 mg for basal losses, 270 mg to the foetus, 90 mg with the placenta and umbilical cord, and about 150 mg as peripartum iron losses (Hardman & Limbird, 2001). These additional requirements are not easily met from the diet, and women

Table 1. Iron absorption in women taking Spatone

Variable	Nonanaemic, nonpregnant women		Anaemic pregnant women	
	Water	Spatone	Water	Spatone
Number	6	15	12	12
Weight (kg)	84 ± 33*	74 ± 19*	74 ± 16*	75 ± 23*
Serum ferritin ($\mu\text{g/l}$)	68 ± 67*	36 ± 11*	6 ± 2*	7 ± 2*
Transferrin saturation (%)	21 ± 10*	27 ± 16*	7 ± 5*	8 ± 4*
Percentage of Fe absorption	0	13.8 ± 7*	0	19.6 ± 7.0*
Percentage of Fe absorption (corrected for the increased plasma volume in pregnancy)	0	–	0	28.2 ± 10.0*

*Values are given as mean ± SD.

who enter pregnancy with a serum ferritin concentration of $<50 \mu\text{g/l}$ are at a high risk of developing iron deficiency anaemia (Romslo *et al.*, 1983) compared with women with serum ferritin $>80 \mu\text{g/l}$.

Oral iron is offered to women with iron deficiency anaemia but this is sometimes difficult to distinguish from the physiological anaemia of pregnancy, a consequence of the expansion in plasma volume. Serum ferritin concentrations are also affected by the changes in plasma volume. Transferrin saturation (the ratio of serum iron and total iron binding capacity) should provide an indicator that is unaffected by changes in plasma volume, but tends to be low in pregnancy because the increased iron requirements cause a greater rate of iron clearance from the plasma. However, the relationship between the maximum increase of serum iron and the absorption of iron was found to be the same in normal and iron deficient subjects (Ekenved *et al.*, 1976).

In the first trimester, iron requirements are less than those of menstruating women (at the basal requirement of 0.8 mg daily) but the daily requirement increases to about 4 mg in the second trimester and 7 mg in the last trimester. All studies of iron absorption in pregnancy show that there is a striking and appropriate increase in percentage absorption as pregnancy proceeds (British Nutrition Foundation, 1995). Studies with radioactive and stable isotopes of iron have shown increases of 5–10-fold for the third trimester compared with the first trimester. If the dietary iron intake of about 12 mg/day is sufficient to provide an adequate iron absorption of about 1 mg/day in the first trimester then a 5-fold increase in absorption should satisfy the requirements during the second and third trimester. However, in many cases this is not achieved, iron balance is negative (Hardman & Limbird, 2001) and supplementation is required if anaemia is to be avoided.

The standard dose of ferrous sulphate for prophylaxis is 65 mg Fe/day and even at a conservative estimate of 10% absorption, this provides sufficient iron to prevent iron deficiency anaemia. However, many women do not continue with oral iron because of side-effects including nausea, epigastric pain, diarrhoea in subjects with inflammatory bowel disease and constipation. Side-effects are much more frequent when three tablets are taken each day (Hardman & Limbird, 2001). The smaller amount of iron in Spatone provides a higher percentage absorption than the larger doses of ferrous sulphate and the incidence of side-effects should be low. None of the participants reported any adverse effects. A previous study indicated that in women with iron deficiency (serum ferritin $<15 \mu\text{g/l}$), a mean of 34% absorption was achieved from

3 mg Fe and in this study, a mean absorption of 28% (range 5–40%) from 25 mg Fe was found. A recent study of Spatone taken in weeks 22–28 of pregnancy by women who had not complied with the standard ferrous sulphate prophylaxis for anaemia has been reported. In women taking Spatone, the fall in serum ferritin concentrations was significantly less than in women not taking iron and there were no differences in the frequency of dyspepsia (McKenna *et al.*, 2002).

During pregnancy, a mean iron absorption of 2.5 mg/day is required if iron stores after birth are not to be reduced below the level of storage iron before pregnancy. To avoid reducing iron stores during later pregnancy, about 4 mg Fe/day is required. It is reasonable to assume that at least 1 mg Fe/day is provided from the diet throughout pregnancy. Mean absorption from two sachets of Spatone (10 mg Fe), in empty stomach, will be between 28% (25 mg dose) and 34% (3 mg dose), and will provide another 3 mg iron for women with low iron stores. This should provide an adequate iron supply for most women. Women who enter pregnancy with iron deficiency anaemia, or an absence of storage iron (serum ferritin $<15 \mu\text{g/l}$) will require supervision and higher doses of supplemental iron to increase the level of storage iron. Doubling the daily dietary iron intake of 11 mg by supplementation should prevent the development of iron deficiency anaemia in most women. This may be provided by taking two sachets of Spatone (10 mg Fe) daily.

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