Analysis

Iron supplementation in women:

impact of frequency on efficacy and tolerability

IRON METABOLISM AND DEFICIENCY

Iron deficiency is a common condition affecting an estimated 11.1% of UK women aged 15–49 years.[1] First-line treatment is generally oral (PO) supplementation, which is also known to cause gastrointestinal (GI) side effects in up to 70% of patients.[2]

Oral iron compounds contain iron in either ferrous or ferric forms.[3] Ferrous iron (Fe2+) is readily absorbed in the duodenum whereas ferric iron (Fe3+) must be reduced to Fe2+ prior to absorption.[3–5] Ferrous salts are iron compounds that include the common preparations ferrous fumarate ($C_4H_2FeO_4$) (organic) and synthetic ferrous sulphate (FeO_4S) (inorganic). Ferrous salts have comparable bioavailability and side effect profiles but contain variable amounts of elemental iron.[3,5] Both preparations are effective iron supplements. After absorption, iron is transported into enterocyte cytoplasm by divalent metal transporter DMT1.[4,6] This is then stored as ferritin or exported into circulation by ferroportin, where it is bound by transferrin allowing for systemic transport.[4,6] Once iron has entered the blood stream there is no active excretion process and therefore iron absorption is carefully regulated.[4,6]

Hepcidin is the main regulator of iron homeostasis[5,7] and high serum hepcidin (sHep) levels reduce bioavailability of PO iron.[6,7] Hepcidin binds to ferroportin receptors on cell surfaces, blocking their effect by endocytosis and degradation.[6–8] Decreased ferroportin function then leaves iron unabsorbed in the GI tract, which may cause inflammation and changes to the gut microbiome, resulting in common GI side effects such as nausea, constipation, diarrhoea, and epigastric pain.[2,5] Oral iron supplementation causes an increase in sHep lasting 24 hours and therefore alternate-day (AD) dosing may be beneficial to increase absorption and reduce side effects.[7,8] Alongside sHep levels, other measures such as haemoglobin (Hb), mean iron, and ferritin levels can all help determine iron absorption and effect.[4,5]

EVIDENCE TO DATE

A randomised controlled trial (RCT) conducted by Kaundal *et al*[9] compared efficacy of AD dosing with twice-daily (BD) dosing using ferrous sulphate in 62 participants over 6 weeks. The control group (n = 31) received 120 mg of elemental iron per day (60 mg BD dosing). The intervention group (n = 31) received 120 mg of elemental iron once daily on alternate days (AD dosing). The primary efficacy endpoint was an increase of 2 g/dl in Hb. The proportion of participants achieving this endpoint was significantly higher in the BD group (32.3%) than in the AD group (6.5%) after 3 weeks of treatment (P<0.0001). After 6 weeks the proportion was 58.0% and 35.5%, respectively (P = 0.001). Interestingly, the proportion of participants achieving 2 g/dl increase in Hb at 6 weeks in the AD group (35.5%) was not significantly different from what was reported in the BD group (32.2%) at 3 weeks (P>0.05). The total dose of elemental iron administered at that stage (AD group = 6 weeks, BD group = 3 weeks) was the same.

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Secondary endpoints included adverse effects and change in sHep. Nausea was more commonly reported in the BD group (38.7%) than in the AD group (22.5%) (P = 0.03), while incidence of other GI side effects was comparable between groups and was reported in <10% of participants. There was no significant change in sHep levels in either group.

A crossover study by Stoffel *et al*[7] compared dose differences between consecutive-day (CD) and AD dosing in 19 participants. Doses of 100 mg ferrous sulphate were administered on days 2, 3, and 5, then 200 mg doses were administered on days 23, 24, and 26 (days 2, 3, and 5 of the second period). Iron absorption was assessed on days 2 and 3 (CD) and day 5 (AD). Fractional iron absorption (FIA) and total iron absorption (TIA) were both higher with AD dosing than with CD dosing (P<0.001). Both doses reported higher sHep levels with CD dosing (day 3 compared with day 2, P<0.01) and lower sHep levels with AD dosing (day 5 compared with day 3, P<0.05). This study followed on from an earlier open-label RCT with 40 participants who were administered either 60 mg of iron on a CD dosing schedule for 14 days (n = 21) or 60 mg of iron every second day for 28 days (n = 19).[10] In this earlier study, both FIA (P = 0.0013) and TIA (P = 0.0010) were higher with AD dosing compared with CD dosing. GI side effects (nausea and abdominal pain) were comparable between the two groups (P = 0.57).[10]

A randomised controlled study by Düzen Oflas *et al*[11] included 150 participants and compared AD, CD, and BD dosing of ferrous sulphate over 1 month. Fifty participants received 80 mg of elemental iron twice daily (total daily dose = 160 mg), 50 received 80 mg daily, and the remaining 50 received 80 mg every other day. Treatment efficacy was assessed by comparing the mean value of Hb, total iron-binding capacity (TIBC), ferritin, and serum iron. The frequency of GI side effects was also reviewed. All three groups had significant increases in mean Hb (P<0.05), mean ferritin, and iron values (P<0.0001), and decreases in TIBC (P<0.0001) compared with baseline measurements. Increases in Hb and decreases in TIBC were comparable between groups (P = 0.09 and P = 0.26, respectively). A significant increase in ferritin was noted in the BD group (29.7 ng/mL; P<0.05) compared with the CD and AD groups (19.5 ng/mL and 19.2 ng/mL, respectively). However, the increase was comparable between CD and AD dosing (P = 0.99). Increases in serum iron values were comparable for BD and CD dosing (75 and 66 µg/dL; P = 0.64) and were both significantly higher than AD dosing (49 µg/dL; P = 0.03). GI side effects were significantly higher in

> *"... iron absorption* [was] *higher with alternative-day dosing than with continuous-day dosing."*

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the BD group, affecting 68% of participants ($P = 0.01$). Participants receiving either CD or AD dosing experienced comparable incidence of GI side effects (12% and 10%, respectively; $P = 0.20$).

A Cochrane review in 2019 investigated intermittent iron supplementation in menstruating women.[12] Eight studies that included 1749 participants reported that intermittent supplementation may provide a comparable effect to daily supplementation in treating anaemia (risk ratio [RR] 1.09, 95% confidence interval [CI] = 0.93 to 1.29) while six studies that included 1166 participants reported 59% less risk of GI side effects with intermittent supplementation when compared with daily dosing (RR 0.41, 95% CI = 0.21 to 0.82).[12]

APPLICATION TO PRACTICE

In summary, two studies reported that AD dosing offered better absorption than CD dosing,[7,10] while another study and meta-analysis concluded that AD dosing may offer comparable efficacy.[11,12] Kaundal *et al*[9] concluded that, while BD dosing achieved study endpoints more quickly, AD dosing reached the same markers soon after. Of note, evidence to date indicated fewer GI side effects with AD dosing.[7,9–12]

Although the overall conclusion is that AD dosing offers similar or better clinical response, further research could provide more certainty. The studies mentioned above include relatively small population groups and differing doses of elemental iron and efficacy measures.

British Society of Gastroenterology (BSG) guidelines recommend treating iron deficiency anaemia with daily PO ferrous sulphate, fumarate, or gluconate that can be reduced to one tablet on alternate days if not tolerated. Liquid or parenteral supplementations could also be considered in this case. Monitoring of Hb levels until normalisation is recommended, followed by an additional 3-month treatment to replenish marrow iron stores (medium-quality evidence, 92% consensus, strong statement strength).[13] Ultimately, either daily or AD treatment options are satisfactory. If a rapid response is required, BD or CD dosing appears to be the pertinent option. However, if gradual replacement is needed or GI side effects impact on patient quality of life then AD dosing may be a suitable option. Prescribers may find that the potential for fewer GI side effects with AD dosing increases patient tolerability and adherence, resulting in improved and sustained clinical outcomes.

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Funding
No funding was received for this research review.

Provenance
Freely submitted; externally peer reviewed.

Competing interests
The authors have declared no competing interests.

DOI: https://doi.org/10.3399/bjgp22X719045

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