

## Review Article

### The misogyny of iron deficiency

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## **Summary**

Anaemia is common, particularly in women and the commonest underlying cause, iron deficiency, is often overlooked. Anaemia is associated with increased morbidity and mortality in patients undergoing anaesthesia; however, women are defined as being anaemic at a lower haemoglobin level than men. In this narrative review, we present the history of iron deficiency anaemia and how women's health has often been overlooked. Iron deficiency was first described as 'chlorosis' and a cause of 'hysteria' in women and initial treatment was by iron fillings in cold wine. We present data in population screening on how common iron deficiency is, affecting 12–18% of apparently 'fit and healthy' women and the commonest cause is heavy menstrual bleeding; both conditions being often unrecognised. We describe a range of symptoms reported by women, that vary from fatigue to brain fog, hair loss and eating ice. We also describe experiments on the physical impact and reduced exercise performance that are related to iron deficiency in skeletal muscle independent of haemoglobin concentration, as well as the impact of iron supplementation in women to improve oxygen consumption and fitness. Overall, we demonstrate the need to single out women and investigate iron deficiency rather than accept the dogma of normality and differential treatment, this is to say the need to change the current standard of care for women undergoing anaesthesia.

“Those diseases which medicines do not cure, iron cures; those which iron cannot cure, fire cures; and those which fire cannot cure, are to be reckoned wholly incurable” (Hippocrates).

Hippocrates described iron deficiency anaemia as a disease that brought about a greenish colour, which caused both headaches and the urge to eat things such as dirt [1]. This “green sickness” was later termed by Johannes Lange in 1554 as ‘chlorosis’ (to define the appearance of anaemia) and was rather misogynistically linked to ‘hysteria’ in women [2-4]. In 1687, Sydenham was accredited as being the first to describe the use of iron filings in cold wine to treat “the green sickness” [1,5]. This treatment remained the standard of care until oral iron supplementation was developed by Blaud in 1832, who introduced pills containing 1.39 g of ferrous sulphate and 0.1 g of potassium carbonate [4,6].

At the turn of the last century, Henry Christian wrote *“a belief in the efficacy of iron as a cure for many ills of the body is found firmly established at a very early period in the development of medicine”* [1]. Today iron deficiency remains the most common nutrient deficiency globally, affecting approximately 2 billion people [7,8] and is the commonest cause of anaemia. Iron deficiency anaemia is particularly common in women [9], due to increased iron loss from menstrual bleeding or increased demand during pregnancy. Approximately one in three women experience heavy menstrual bleeding, of whom half may subsequently have iron deficiency [7]. Indeed, iron deficiency is so common in women that it can be regarded as ‘hiding in plain sight’, so much so that the original World Health Organization definition of anaemia, being a haemoglobin concentration < 120 g.l<sup>-1</sup> in women compared to < 130 g.l<sup>-1</sup> in men, was ‘arbitrary’ at best [10-12].

The normal range of haemoglobin was determined from the distribution in healthy population groups, whereby an arbitrary proportion of the healthy population (usually 2.5%) is assumed to fall below the appropriate threshold. The variation in haemoglobin values in healthy human beings is relatively large; in women aged 18–50 years mean haemoglobin is 140 g.l<sup>-1</sup>, whilst the value two standard deviations (SD) below the mean is 120 g.l<sup>-1</sup>, a difference of about 14%. However, this does not account for the fact that 10–14% of women have iron deficiency. Therefore, by including those with iron deficiency in the ‘healthy population’, the resultant ‘normal distribution’ would be skewed. This may account for the considerable variation in reference intervals seen in laboratories for iron deficiency [13] and anaemia [14] that, according to the Clinical Laboratory Standards Institute guideline EP28-A3c, can be based on a minimum sample size of only 120.

This is relevant to the care of women undergoing anaesthesia [10]. By accepting a lower (standard of care) reference for the definition of anaemia in women, i.e. haemoglobin  $10 \text{ g.l}^{-1}$  lower than that for men, we may be missing problems in women that could affect outcome. A woman with haemoglobin of  $121 \text{ g.l}^{-1}$  would be regarded as normal, whereas a man with the same result would be regarded as having mild anaemia and be investigated accordingly, with increased awareness that even mild anaemia is associated with increased patient morbidity, complications, length of hospital stay and mortality [15]. In the large associative analysis of anaemia and outcomes after surgery there is no sex differential with risk increasing with haemoglobin levels  $< 130 \text{ g.l}^{-1}$  (haematocrit  $< 36\%$ ) [16]. After all, the indication for blood transfusion (haemoglobin  $< 70\text{--}80 \text{ g.l}^{-1}$ ) is not differentiated by sex. When adopting equal reference ranges, women are more likely to have iron deficiency [17] that again may be associated with immediate and long-term negative outcomes [18], they may also be likely to gain from appropriate investigation and treatment [19,20].

Here we investigate the prevalence of iron deficiency and anaemia in the 'fit and healthy' population of women, the range of symptoms experienced by women, and the potential impact on cardiovascular fitness. A series of studies were performed to assess the prevalence of anaemia and iron deficiency in the population of otherwise healthy women, the symptoms of iron deficiency experienced by women and the impact of iron deficiency on physical performance.

### **Prevalence of anaemia and iron deficiency in the population of otherwise healthy women**

A summary of iron deficiency and anaemia in women is reviewed in a parallel manuscript in this supplement. We present novel data on the use of a screening tool for iron deficiency and anaemia in the apparently healthy female population.

A female health questionnaire was developed that comprised questions about risk factors for iron deficiency and anaemia (online Supporting Information Appendix S1), and included a validated four-part diagnostic criterion used to identify the symptom of heavy menstrual bleeding [21]. The symptom of heavy menstrual bleeding was present if two or more of the following criteria were reported: passing of large blood clots; need for double sanitary protection (both towels and tampons); need for frequent changes of protection (getting up at night, changes every 2 h or more than 12 items per cycle); and/or flooding (or fear thereof) through clothes or bedding.

We previously reported questionnaire outcomes from elite and non-elite athletes via social media and at the 2015 London Marathon [22]. The outcomes revealed that, contrary to the perception that

athletes had amenorrhoea, heavy menstrual bleeding was common, affecting 1 in 3 'healthy' female marathon runners. This was as common a problem in elite as non-elite athletes [22], of whom only a small proportion had sought medical advice (22%).

To assess the prevalence of anaemia and iron deficiency in 'healthy female populations', and to identify a population at higher risk, we used the female health questionnaire augmented by haemoglobin finger prick testing (HemoCue® Hb 201+, HemoCue, Radiometer, Crawley, UK). In addition, where anaemic, formal blood testing was performed for laboratory-based haemoglobin and ferritin levels.

The first cohort of 300 apparently 'fit and healthy' women was randomly screened by two staff at a large UK fitness show. Mean (SD) age was 31.2 (7.7) years, mean (SD) haemoglobin was 131.8 (11.5) g.l<sup>-1</sup>. Thirty-six out of 300 (12%) demonstrated anaemia, defined as haemoglobin < 120 g.l<sup>-1</sup> on finger prick testing. Anaemia was more common in those reporting heavy menstrual bleeding (16.5 vs. 9.1%), and heavy menstrual bleeding was a significant predictor of anaemia ( $\beta = 0.80$ ,  $p = 0.03$ ). In addition, those with heavy menstrual bleeding were significantly more likely to report days off work in the last year (39.4 vs. 18.2%;  $p < 0.001$ ).

In a second cohort, female nurses were assessed over two days at the Royal College of Nursing Annual General Meeting. Of 272 who participated, mean (SD) age was 40.1 (13.2) years. Thirty-six of the 272 (13.2%) had anaemia (defined as haemoglobin < 120 g.l<sup>-1</sup>) of whom 16 (44%) reported heavy menstrual bleeding. In total, 72 nurses (26.4%) had a screening haemoglobin < 130 g.l<sup>-1</sup> on finger prick test and were invited for formal laboratory testing. Of these 72 tested, 36 (50%) had an indicator of iron deficiency (ferritin < 30 ng.ml<sup>-1</sup> in 25 nurses (35%), transferrin saturations < 20% in an additional 11 nurses (15%)). Iron deficiency was seen in 25 (69.4%) of those with a finger prick haemoglobin < 120 g.l<sup>-1</sup> and 11 (30.5%) of those with a finger prick haemoglobin 120–130 g.l<sup>-1</sup>, i.e. those who would be defined as 'anaemic' if male but regarded as 'normal' as females.

A third cohort was undertaken, comprising 271 women undertaking a 5 km, 10 km or half marathon running event in Singapore. Mean (SD) age of this cohort was 36.3 (9.6) years. All women completed the female health questionnaire and laboratory analysis for haemoglobin and serum ferritin. Fifty-one of the 271 women (18.8%) had anaemia (defined as haemoglobin < 120 g.l<sup>-1</sup>), but iron deficiency (defined as a serum ferritin < 30 ng.ml<sup>-1</sup>) was far more common, seen in 130 women (48%) tested. Overall, 22.1% of the women in this cohort reported heavy menstrual bleeding. Those with heavy

menstrual bleeding were twice as likely to suffer anaemia (28.3% vs. 16.1%;  $p < 0.05$ ) and have severe iron deficiency (defined as ferritin  $< 15 \text{ ng.ml}^{-1}$ ; 48.3% vs. 25.1%,  $p < 0.05$ ).

Data from this series of cohorts suggest that screening for anaemia and iron deficiency is worthwhile. Although there may be selection and detection bias in the women participating, the results suggest that anaemia is common in apparently fit and healthy women with a prevalence of 12–18% and that up to 1 in 3 women may have undiagnosed iron deficiency. Based on the questionnaires used in these studies the most common identified clinical association was the symptom of heavy menstrual bleeding. These data also validate the use of a simple questionnaire augmented by finger prick haemoglobin to identify women at higher risk of anaemia and iron deficiency. These simple 3–4 min assessments could be utilised to screen apparently fit and healthy women and similarly could be considered as a pre-operative screening assessment for (both staff and patients) in anaesthesia.

### **Symptoms of iron deficiency experienced by women**

It is important to understand that symptomatic iron deficiency can occur without anaemia. Iron is an essential trace mineral that plays a role in many organismal and cellular processes in addition to the transport of oxygen by haemoglobin. Iron is important for mitochondrial energy metabolism, and a large number of enzymatic processes across multiple tissue sites affecting function in myocardial and skeletal muscle, neurotransmitter production and the immune system (T-cell activity in particular) [23,24].

As iron deficiency develops, iron is initially utilised from stores (ferritin) predominantly in the liver but subsequently sequestered from these iron-enzymes and iron-proteins in tissue in an attempt to preserve erythropoiesis [23,25,26]. Consequently, symptoms relating to iron deficiency can be diverse, relating to depletion of cellular iron function in multiple tissue types, and exist long before prolonged iron deficiency restricts haemoglobin synthesis in the bone marrow and anaemia develops. Whilst there is overlap in the common symptoms of iron deficiency and anaemia: fatigue, lethargy, dizziness, and shortness of breath; these symptoms of loss of concentration, headaches and easy bruising are more indicative of iron deficiency and a few symptoms are highly specific to iron deficiency such as restless leg syndrome, hair loss or pica (inexplicable eating of ice, paper or dirt) [27-29].

To assess the range and prevalence of symptoms experienced by women with iron deficiency [30] we undertook a consumer involvement exercise through social media. Initially a poll was developed to ask women about their symptoms in their own words. Responses were collated and returned as part of a short questionnaire to ask about women's symptoms and experiences with iron deficiency. The initial poll returned a total of 10,521 responses describing 75 symptoms. Subsequently, 457 individuals undertook a second-round detailed questionnaire. The commonest 5 symptoms described in decreasing frequency were 'fatigue', 'exhaustion', 'brain fog', 'muscle weakness' and 'shortness of breath' (Fig. 1). This highlighted the novel symptom of 'brain fog' (described by patients to be the inability to think clearly, concentrate or focus. Brain fog was also described by some responders interchangeably as 'mummy brain'.) Median (IQR) [range] duration of symptoms was 4 (2–10) [0–44] years with median (IQR) self-reported ferritin of 7 (5–13) [1–87]  $\mu\text{g.l}^{-1}$  and median (IQR) haemoglobin of 100 (IQR 80–120) [3–17]  $\text{g.l}^{-1}$ . Ninety-one percent of respondents had taken oral iron supplementation for a median (IQR) of 6 (2–14) months, with 72% experiencing side effects and, as a result, 45% discontinued treatment.

### **Impact of iron deficiency on physical performance**

The link between iron deficiency and fitness has been recognised for millennia. Roman soldiers wounded after battle were described adding the rust from their bloodied swords to food, mythologically linking Mars, the God of war, and his metal, iron. More quantifiable physiological assessment of anaemia and functional capacity was seen in descriptive analyses of female tea pluckers in Sri Lanka. In the initial research by Selvaratnam et al. [31] of 304 tea pluckers, 94.4% were anaemic, with an overall mean monthly productivity of 275.5 kg of tea leaves. Variation in haemoglobin accounted for a 65% variation in productivity, such that an increase in haemoglobin of  $10 \text{ g.l}^{-1}$  was associated with an increase in monthly productivity of 73 kg. Edgerton et al. [32], in a separate paired placebo controlled trial of 217 female workers with anaemia, also showed that iron supplementation increased productivity. There was a correlation between female worker productivity with haemoglobin, with an increase of 0.75 kg of tea per day per  $10 \text{ g.l}^{-1}$  haemoglobin rise.

### **Iron and muscle function**

The interplay between iron deficiency and anaemia on functional performance was assessed in an animal model. Exercise capacity was measured comparing treadmill performance in a group of control rats fed normal chow with an experimental group with iron deficiency anaemia created by an iron deficient diet [33]. Those animals with iron deficiency anaemia had reduced running time

compared to controls. Subsequently, those animals with iron deficiency anaemia were randomly allocated to continued iron deficient diet, iron supplementation diet or blood transfusion, and compared with the normal controls using the same treadmill test. Iron supplementation improved running times to near the normal maximum levels of the controls within three days, notably before correction of the anaemia. In comparison, such an improvement was not seen in rats with iron deficiency anaemia who underwent blood transfusion. These results indicated that it was the iron deficiency and subsequent iron supplementation that impacted running times, not the anaemia (or blood transfusion). Laboratory analysis showed reduced mitochondrial complex III and a decrease in complex I enzyme activity in skeletal muscles with iron deficiency [34].

Energy production, or adenosine triphosphate synthesis, takes place in the mitochondrial electron transport chain, where a charged gradient is created across the membrane, which in turn drives the synthesis of adenosine triphosphate. Shifting charged particles to create this gradient requires a stepwise, rapid accepting and releasing of electrons from one mitochondrial complex to another. Both haem and non-haem iron proteins are pivotal due to the ability of iron to shift from ferrous to ferric states. All the protein complexes within the electron transport chain contain iron with haem-containing proteins in complexes II, III and IV, and iron-sulphur cluster proteins in complexes I, II and III [34]. The mitochondria is one of the most iron-rich organelles in the body [35]. Skeletal muscle contains 10–15% of the body's iron [36] that is particularly concentrated in type I slow twitch muscle fibres. These fibers have high mitochondrial content, slow contraction rates and a reliance on aerobic metabolism and oxidative phosphorylation. Type II, fast twitch fibres, are characterised by lower mitochondrial content, rapid contractions, lesser reliance on oxidative phosphorylation, and more on glycolytic energy production [37].

To reproduce these early experiments on functional performance, the impact of iron deficiency was assessed in mice, using an iron-depleted (2–6 ppm of iron) diet (Teklad Custom Diet, Envigo, Huntingdon UK). The control group was fed a normal diet (iron at 48 ppm). Weight and haemoglobin (through tail vein samples, HemoCue 201+, HemoCue, Radiometer, Crawley, UK) were assessed weekly. Following a period of training and acclimatisation, running time to exhaustion was assessed using a treadmill with increasing speed on a weekly basis. Anaemia, defined as haemoglobin < 136 g.l<sup>-1</sup> [38], occurred after 8 weeks, when the experimental animals were randomly allocated a single injection of either placebo (normal saline) or one of the following intravenous iron preparations, ferric carboxymaltose (Vifor Pharma, Staines, UK, n = 10) or iron isomaltoside (Pharmacosmos,



Holbæk, Denmark, n = 10). Running times to exhaustion were then examined at 24, 48 and 72 h post infusion.

Iron deficiency led to reduced mean running time to exhaustion (mean difference = 8.74 min, q ratio = 11.5,  $p < 0.0001$ ), which returned to normal within 72 h of either iron infusion compared to placebo (Fig 2). The speed of this return suggests a direct causal relationship between iron deficiency and skeletal muscle function, as the results were independent of haemoglobin concentrations; control  $150 \text{ g.l}^{-1}$  (2.67) vs. iron deficient  $134 \text{ g.l}^{-1}$  (2.0) vs. ferric carboxymaltose  $135 \text{ g.l}^{-1}$  (1.7) vs. iron isomaltoside  $130 \text{ g.l}^{-1}$  (1.8),  $p < 0.001$ ).

### **Iron in athletes**

One problem with human trials on iron supplementation with endpoints of symptom improvement or physical performance is that they are inherently confounded, as the intervention is iron, whereas the endpoint is often the assessment of anaemia. Therefore, it is not clear whether it is the iron supplementation or the correction of anaemia that causes the improvements. Data on the impact of iron deficiency and iron supplementation in exercise performance are heterogeneous [18]. A cohort study in highly trained female distance runners with low iron status (serum ferritin  $< 35 \text{ ug.l}^{-1}$  and transferrin saturation  $< 20\%$  or serum ferritin  $< 20 \text{ ug.l}^{-1}$  alone) showed that intravenous iron therapy (but not oral iron) resulted in increased oxygen consumption ( $\text{VO}_2 \text{ max } 59.0 \pm 10.8 \text{ ml.kg}^{-1} \cdot \text{min}^{-1}$  to  $61.7 \pm 6.8 \text{ ml.kg}^{-1} \cdot \text{min}^{-1}$ ), which was associated with an increase in total haemoglobin mass (mean increase  $+ 4.9\%$ , 90%CI  $1.1\%–8.9\%$ ) [39]. Contrastingly, in a randomised controlled trial in elite mixed sex distance runners with a serum ferritin value of  $< 30 \text{ ug.l}^{-1}$  for females and  $< 40 \text{ ug.l}^{-1}$  for males, a single dose (500 mg) of intravenous iron had no difference in outcomes of maximum rate of oxygen consumption ( $\text{VO}_2 \text{ max}$ ), running economy, time to exhaustion or total haemoglobin mass between groups [40] compared with placebo.

The heterogeneity of outcomes from clinical trials of iron supplementation in athletes has confounded the results of meta-analysis [18,41,42]. There appear to be several reasons: mixing men and women into the same population; studies with small samples of highly trained athletes where gains in performance may only be marginal ( $< 5\%$ ) and therefore not significant and the inconsistent diagnostic criteria for iron deficiency (variable ferritin cut offs between  $12–50 \text{ ug.l}^{-1}$ ). However, when looking at those clinical trials involving only women with iron deficiency (defined as ferritin  $< 15–20 \text{ ug.l}^{-1}$ ), the data appears more consistent with improvements seen in endpoints of fatigue, cognition, time to exhaustion and maximal oxygen consumption ( $\text{VO}_2 \text{ max}$ ) [43]. The study by Favrat

et al. randomly allocated women with iron deficiency to placebo or a single dose (1000 mg) of ferric carboxymaltose and showed improved fatigue scores, mental quality of life and cognitive function [44]. In a placebo-controlled RCT of female volleyball players with iron deficiency, those randomised to 200 mg of ferrous sulphate taken daily for 2-months had improved maximal oxygen consumption ( $VO_2$  max) scores ( $45.98 \pm 1.76$  vs.  $42.40 \pm 1.22$  ml.kg<sup>-1</sup>.min<sup>-1</sup>;  $p < 0.001$ ). A meta-analysis of female only populations showed that iron supplementation improved exercise performance [45]. These data again reinforce the notion that clinical trials on iron deficiency should be designed to assess women separately as the causality and impact of iron deficiency on health-related outcomes are different in men and women.

### **Conclusion**

Iron deficiency is common even in apparently healthy women. The impact of iron deficiency is independent of haemoglobin levels and is associated with a multitude of symptoms that affect both mental and physical health as well as work productivity. Treatment of iron deficiency can improve skeletal muscle function and physical function, particularly in women, so if the target haemoglobin for optimal health is 140 g.l<sup>-1</sup> then there is a need to single out women and investigate iron deficiency rather than accept the dogma of normality and differential treatment. Consideration of routine measurement of ferritin and haemoglobin in reproductive aged women should be on the agenda of all health care provider systems.

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### **Online Supporting Information**

#### **Appendix S1: Female Health Questionnaire**

## Figure legends

Figure 1 Symptoms of iron deficiency reported by 457 women.

Figure 2. Effect of iron-depletion and iron repletion on endurance in mice. Time to exhaustion while running on a treadmill was measured in control and iron deficient diet fed mice. After 7 weeks, iron deficiency animals were randomly allocated to intravenous iron isomaltoside, ferric carboxymaltose or placebo and reassessed at 24, 48 and 72 h post-injection. (Work by Dr Anna Butcher)