



Iron Deficiency Without Anaemia in Menstruating Women: A Case for Screening Before the Haemoglobin Falls

Nadia Belhadj^{1*}, Cecilia Marchesini² and Roos Timmermans³

¹Department of Haematology, Alsace Centre for Metabolic Nutrition, Strasbourg, France

²Department of Clinical Nutrition, Abruzzo University Hospital, Pescara, Italy

³Department of General Practice, Twente University Medical Centre, Enschede, Netherlands

*Correspondence to: Nadia Belhadj, Department of Haematology, Alsace Centre for Metabolic Nutrition, Strasbourg, France

E-mail: n.belhadj@acmn.fr

Received: 01 February 2022; Accepted: 07 June 2022; Published: 26 September 2022

Copyright: © 2022 Belhadj N, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Iron deficiency develops long before haemoglobin falls, and the tests used routinely detect the anaemia rather than the deficiency. Among 114 young women referred with heavy menstrual bleeding, 58 had ferritin below 20 ng/mL and only 24 of those, 41.4 per cent, were anaemic. Haemoglobin alone identified iron deficiency with a sensitivity of 41.4 per cent and the full blood count with 46.3 per cent, against specificities of 91.1 and 83.9 per cent. A test that misses more than half of cases is not a screening test for this condition. The case for measuring ferritin is therefore strong on detection, and two things qualify it. The threshold is unsettled, with 15, 20, 30 and 50 ng/mL all in current use and a guideline panel suggesting 30 on low certainty evidence. And in a randomised comparison of supplementation against a high-iron diet in 44 women, vitality and mental health improved in both arms while ferritin rose more with supplement alone.

Keywords: Iron deficiency; Ferritin; Menstruation; Screening; Fatigue

Introduction

Iron depletion proceeds in stages. Stores fall first, then transport iron and erythropoiesis are affected, and only at the end does haemoglobin drop below the threshold for anaemia [1,2,3]. A woman can therefore be substantially iron deficient with an entirely normal full blood count.

Menstruating women lose iron monthly and are among the groups in whom deficiency is most common, with prevalence in industrialised countries reported between 4 and 33 per cent [4,5,21]. The relationship between heavy menstrual bleeding, deficiency and anaemia has been set out directly [21], and clinical guidelines on managing it in that population have been reviewed [22]. Symptoms attributed to deficiency without anaemia include fatigue, reduced exercise tolerance, impaired cognition and restless legs [1,6,7,17]. Deficiency without anaemia has been associated with anger and fatigue in young women [17], and with reduced quality of life in those with heavy

menstrual bleeding [18].

This review examines how much deficiency the routine tests miss, which threshold defines the condition, and what the randomised evidence shows about treating it.

Objective

The purpose of this review is to establish three things from the published literature. First, the performance of haemoglobin and the full blood count as tests for iron deficiency in menstruating women. Second, which serum ferritin threshold is supported, and on what strength of evidence. And third, whether treating deficiency in the absence of anaemia improves symptoms in randomised comparison.

Literature Review

What the routine tests miss: A retrospective review examined 114 young women aged 9 to 19 consecutively referred to a young women's haematology clinic with heavy menstrual bleeding. Fifty-eight, or 50.9 per cent, had ferritin below 20 ng/mL indicating iron deficiency. Of those 58, only 24, or 41.4 per cent, were anaemic and 25, or 46.3 per cent, were microcytic (Figure 2) [8].

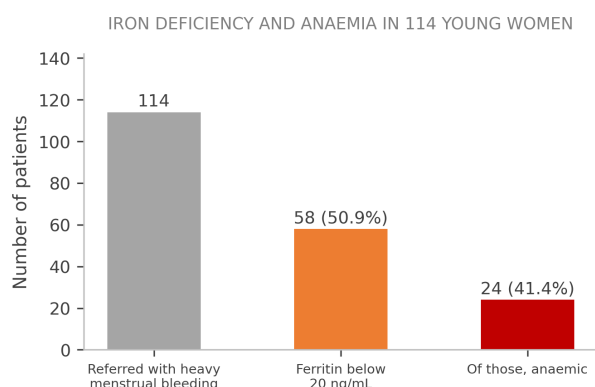


Figure 2: Iron deficiency and anaemia in 114 young women referred with heavy menstrual bleeding [8]

Sensitivity and specificity: In the same cohort, the sensitivity of haemoglobin alone for identifying women with ferritin below 20 ng/mL was 41.4 per cent (95% CI 28.7 to 54.1), and of the full blood count alone 46.3 per cent (33.0 to 59.6). Both had reasonable specificity, at 91.1 per cent (83.6 to 98.5) for haemoglobin and 83.9 per cent (74.3 to 93.6) for the full blood count (Figure 1) [8].

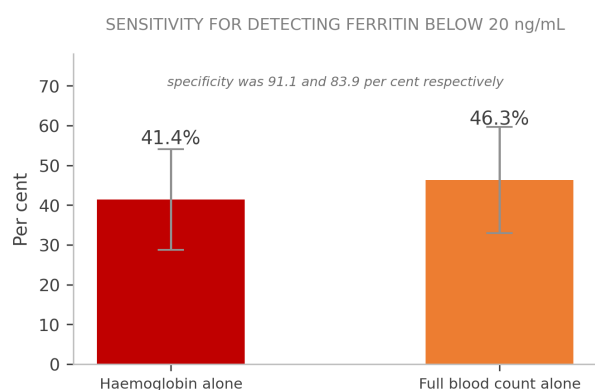


Figure 1: Sensitivity of routine tests for detecting ferritin below 20 ng/mL [8]

Table 1: Performance of routine tests against ferritin below 20 ng/mL in 114 young women [8]

Test	Sensitivity	Specificity
Haemoglobin alone	41.4% (28.7 to 54.1)	91.1% (83.6 to 98.5)
Full blood count alone	46.3% (33.0 to 59.6)	83.9% (74.3 to 93.6)

The threshold is unsettled: Conventional criteria have used serum ferritin thresholds of below 30 ng/mL, and more recently below 50 ng/mL has been proposed [9,10]. A diagnostic algorithm for otherwise healthy people sets 30 micrograms per

litre as appropriate for males and females above 15 years, with 15 and 20 micrograms per litre for children aged 6 to 12 and adolescents aged 12 to 15 respectively (Figure 3) [11]. A guideline panel developing diagnostic recommendations suggests a threshold of 30 ng/mL or below in menstruating individuals and suggests against 15 ng/mL or below, describing this as a conditional recommendation based on low certainty in the evidence [12].

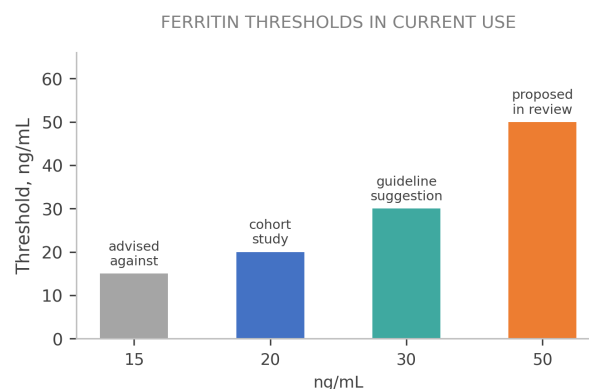


Figure 3: Serum ferritin thresholds in current use [9,10,11,12]

Why no threshold resolves it: Reviews of this condition state plainly that it is not easy to diagnose, and that any chosen cut-off value for the diagnostic parameters of iron status will have either low specificity or low sensitivity (Figure 4) [6]. Ferritin is additionally an acute phase reactant, so an inflammatory response produces falsely reassuring values, and diagnostic algorithms recommend excluding this by history and C-reactive protein measurement [11,24]. Meta-analysis has quantified how far plasma ferritin requires adjustment for subclinical inflammation [24], and international guidance on using ferritin to assess iron status addresses the same problem [26,27]. Quantitative assessment of body iron using paired measures has been proposed as an alternative [23,25].

Who is suggested for testing: The same algorithm recommends a baseline set of blood tests including haemoglobin, haematocrit, mean cellular volume, mean cellular haemoglobin, percentage of hypochromic erythrocytes and serum ferritin in symptomatic patients with fatigue and in populations at risk, defined as adolescence, heavy or prolonged menstruation, high-performance sport, vegetarian or vegan diet, eating disorder and underweight (Figure 6) [11].

Table 2: Serum ferritin thresholds and the basis for each

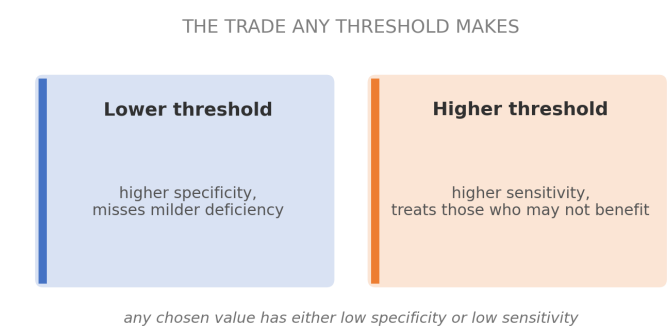


Figure 4: The trade any threshold makes [6,11]

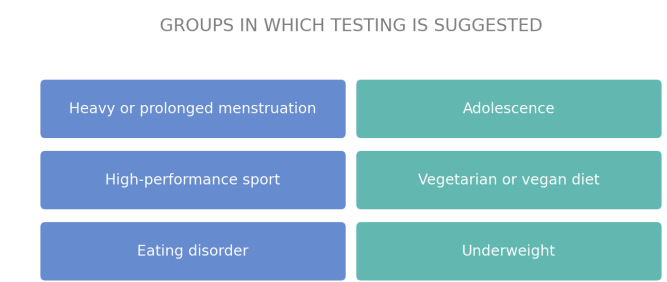


Figure 6: Groups in which testing is suggested [11]

What treatment achieves: Randomised trials have examined iron supplementation for unexplained fatigue in non-anaemic women, including oral supplementation in primary care, oral iron in non-anaemic menstruating women with low ferritin, and intravenous iron in non-anaemic premenopausal women [13,14,15]. Improved aerobic capacity assessed by maximal oxygen uptake has also been associated with supplementation in women with deficiency in the absence of anaemia [6,16]. A systematic review of randomised trials examined fatigue and physical capacity in non-anaemic iron-deficient adults specifically [31], and Cochrane reviews cover daily and intermittent supplementation in menstruating women [29,30]. Trials in pregnancy address a related but distinct question [19,20].

An important qualification: In an Australian study, 44 women with deficiency and ferritin below 20 micrograms per litre were randomly allocated to iron supplementation or a high-iron diet for 12 weeks. Mental health and vitality scores increased in both intervention groups, while ferritin increased more under supplementation (Figure 5) [6]. The symptomatic improvement was therefore not confined to the arm in which iron stores rose most.

How the iron is given: Tolerability shapes whether treatment is completed. Ferrous sulfate has been reported to cause significant gastrointestinal side effects in adults in systematic review and meta-analysis [32], and absorption studies comparing consecutive with alternate-day dosing found the latter increased fractional absorption [33]. Guidance on diagnosis and treatment sets out where oral and intravenous routes each apply [34].

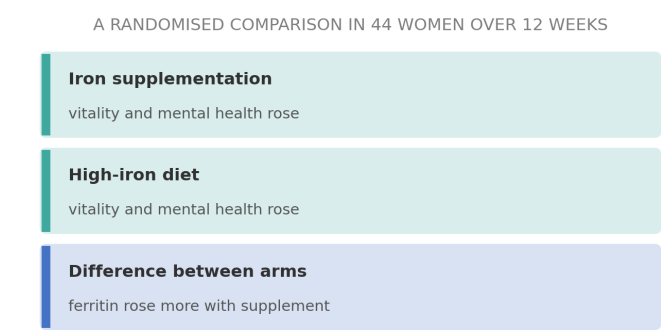


Figure 5: A randomised comparison in 44 women over 12 weeks [6]

Threshold	Source and status
15 ng/mL	Guideline panel suggests against in menstruating individuals [12]
20 ng/mL	Applied in the referral cohort described above [8]
30 ng/mL	Guideline suggestion and diagnostic algorithm [11,12]
50 ng/mL	Proposed in a recent review [10]

Table 3: Where in the sequence each test becomes positive

Stage of iron depletion	What it shows
Stores fall	Ferritin drops; haemoglobin normal [1,2]
Erythropoiesis becomes restricted	Transferrin saturation falls [2,19]
Anaemia develops	Haemoglobin drops below threshold [1]
Detected by routine testing	Only at the third stage [8]

Measuring ferritin reliably: International guidance addresses the use of ferritin concentrations to assess iron status in individuals and populations [18], and reviews have set out what is required to interpret a value correctly [19,20]. Because concentrations rise with inflammation, meta-analysis has examined how to adjust for subclinical inflammation when assessing deficiency [21], and Cochrane review has assessed ferritin as an index of deficiency and overload [20]. Physiologically based thresholds derived from national survey data have been proposed as an alternative to consensus cut-offs [10].

Method

Search strategy: PubMed and the archives of the major haematology, clinical nutrition and general practice journals were searched for studies of iron deficiency without anaemia. Search terms combined iron deficiency without anaemia and non-anaemic iron deficiency with ferritin threshold, menstruating women, screening, fatigue and randomised trial. Reference lists of the diagnostic algorithm [11] and the guideline panel document [12] were screened by hand for primary sources.

Eligibility: Studies were included if they reported the performance of diagnostic tests for iron deficiency in defined

populations, proposed or evaluated a ferritin threshold, or tested treatment against a comparator. Guideline and consensus documents are cited for the recommendations they contain and identified as such.

Data extraction and handling: Population, the ferritin threshold applied, the comparator and the reported estimate were extracted as published. The threshold is stated alongside every prevalence and performance figure, because thresholds of 15, 20, 30 and 50 ng/mL are all in current use and the choice determines both how many people are identified and how the tests perform against them. This review reports published findings and the content of existing guidance. It does not recommend screening, testing or iron treatment for any individual, all of which are matters for the treating clinician. No pooling or re-analysis was performed. Figures 1 to 6 and Tables 1 to 3 reproduce published values only. This is a narrative synthesis of published literature and was not registered as a systematic review.

Concluding Remarks

The detection argument in the title is the strongest part of this case and the numbers make it plainly. In a population selected for heavy menstrual bleeding, half had ferritin below 20 ng/mL and fewer than half of those were anaemic [8]. Haemoglobin identified 41.4 per cent of them. A test with that sensitivity is a test for anaemia, which is what it was designed for, and it is being used as though it were a test for iron status.

The specificity figures point the same way from the other direction. At 91.1 per cent for haemoglobin, a low value is informative when it appears; the problem is that it usually does not appear until the deficiency is advanced [8]. Relying on it means waiting for the last stage of a process that has been running for months.

Two things temper the case. The first is that no threshold settles the question. Fifteen, twenty, thirty and fifty ng/mL are all in current use, a guideline panel suggests thirty while explicitly advising against fifteen, and it grades that recommendation as conditional on low certainty evidence [10,11,12]. Reviews of the condition state that any cut-off will have either low specificity or low sensitivity [6]. Moving from haemoglobin to ferritin improves detection substantially; it does not produce a clean dividing line.

The second is the randomised comparison in 44 women, where vitality and mental health improved in both the supplementation and the high-iron diet arms while ferritin rose more with supplementation [6]. If the symptomatic benefit appears where the biochemical response is smaller, then part of it is not attributable to the change in iron stores. That does not undermine treating deficiency, but it does caution against reading symptom improvement as confirmation that the deficiency caused the symptoms.

A practical consequence follows for how testing is framed. Ferritin is an acute phase reactant, so a normal value in an unwell or inflamed patient does not exclude deficiency, and the diagnostic algorithm accordingly pairs it with C-reactive protein [11]. A screening approach built on ferritin alone inherits a false negative in exactly the patients most likely to be tested for other reasons.

Two limitations belong with these conclusions. The performance figures derive from 114 young women referred to a specialist clinic with heavy menstrual bleeding, which is a high-prevalence population, so sensitivity and specificity would differ in unselected primary care [8]. And the randomised evidence on symptoms is drawn from small trials with differing entry thresholds, iron preparations and outcome instruments, which is why the benefit remains described as controversial in the trial literature itself [4,13,14].

There is a measurement question underneath all of this that the threshold debate tends to obscure. Ferritin is an indirect index of stores, and its interpretation requires adjustment where inflammation is present, which meta-analysis has quantified [24,25]. International guidance now addresses how the measure should be used to assess iron status in individuals and populations, and a Cochrane review has assessed its diagnostic accuracy for deficiency and overload [26,27]. The question is not only where to draw the line but how reliably the quantity being measured reflects what the line is meant to separate.

Finally, a note on treatment that follows from detection rather than preceding it. If ferritin testing is extended, more women will be identified, and the tolerability of what is offered then matters at scale. Ferrous sulfate produces significant gastrointestinal effects in a substantial proportion of adults, and alternate-day dosing has been shown to increase fractional absorption relative to consecutive daily dosing [32,33]. A screening policy that identifies more people without addressing how they are treated will convert a detection gap into an adherence one [29,30,34].

A further point concerns what happens after a positive result. Oral iron is effective and safe in most patients and is the usual first step [4,29]. Where it fails or is not tolerated, intravenous preparations have been compared with oral iron in persistent deficiency [28], and single-dose intravenous treatment has been trialled specifically in fatigued non-anaemic women [7,15]. The choice between them is a clinical decision that this review does not address.

Finally, a note on the population these figures describe. The cohort reviewed here consisted entirely of young women referred to a specialist clinic with heavy menstrual bleeding, in whom half had ferritin below 20 ng/mL [8]. The relationship between heavy menstrual bleeding, iron deficiency and anaemia has been examined directly [22,24], and heavy bleeding is common enough in European survey data that the group is large [23]. Applying the same sensitivity figures to unselected

menstruating women would overstate what the test misses, because fewer of them are deficient to begin with [25,26].

A wider observation about the evidence base. Systematic review of randomised trials of iron supplementation on fatigue and physical capacity in non-anaemic iron-deficient adults exists [26], as does Cochrane review of daily iron supplementation in menstruating women [25], and guidance on diagnosis and treatment across indications has been synthesised [27]. The disagreement described in this review is therefore not for want of trials; it concerns where to place a threshold on a continuous variable and how much symptom benefit follows from crossing it [4,11,26].

On that question the physiology is more settled than the clinical evidence. Iron is required for immune function, muscle metabolism and neuronal functioning [32], and the relationship between deficiency and reduced work capacity has been critically reviewed [33]. Supplementation improved progressive fatigue resistance during dynamic exercise in iron-depleted non-anaemic women [16]. What remains uncertain is not whether iron matters below the anaemia threshold but at which concentration the deficit becomes worth correcting [4,34].

Acknowledgements

The authors thank the investigators who reported test performance against a ferritin reference rather than reporting prevalence alone, which is what makes the size of the detection gap measurable.

Funding

No dedicated funding from public, commercial or charitable sources supported the preparation of this review.

Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

References

1. Pasricha SR, Tye-Din J, Muckenthaler MU, Swinkels DW. "Iron deficiency". *Lancet* 397(2021):233-248.
2. Camaschella C. "Iron deficiency". *Blood* 133(2019):30-39.
3. Lopez A, Cacoub P, Macdougall IC, Peyrin-Biroulet L. "Iron deficiency anaemia". *Lancet* 387(2016):907-916.
4. PREFER investigators. "Evaluation of a single dose of ferric carboxymaltose in fatigued, iron-deficient women: PREFER, a randomized, placebo-controlled study". *PLoS One* 9(2014):e94217.
5. Miller JL. "Iron deficiency anemia: a common and curable disease". *Cold Spring Harb Perspect Med* 3(2013):a011866.
6. Indications for treatment authors. "Iron deficiency without anemia: indications for treatment". *Gastroenterol Rev Med* 4(2020):112-120.
7. Bruner AB, Joffe A, Duggan AK, Casella JF, Brandt J. "Randomised study of cognitive effects of iron supplementation in non-anaemic iron-deficient adolescent girls". *Lancet* 348(1996):992-996.
8. Heavy menstrual bleeding investigators. "Iron deficiency without anemia: a common yet under-recognized diagnosis in young women with heavy menstrual bleeding". *J Pediatr Adolesc Gynecol* 29(2016):628-631.
9. Martens KL, DeLoughery TG. "Sequestered in iron: diagnosis and management of iron deficiency". *Hematology Am Soc Hematol Educ Program* 2023(2023):617-622.
10. Ferritin reference range investigators. "Ferritin reference ranges and improving diagnosis of iron deficiency without anemia". *Blood* 146(2025):2609.
11. Swiss algorithm authors. "The treatment of iron deficiency without anaemia (in otherwise healthy persons)". *Swiss Med Wkly* 147(2017):w14434.
12. American Society of Hematology Guideline Panel. "ASH draft recommendations for diagnosis of iron deficiency". American Society of Hematology, Washington DC (2025).
13. Verdon F, Burnand B, Stubi CLF, Bonard C, Graff M, Michaud A, et al. "Iron supplementation for unexplained fatigue in non-anaemic women: double blind randomised placebo controlled trial". *BMJ* 326(2003):1124.
14. Vaucher P, Druais PL, Waldvogel S, Favrat B. "Effect of iron supplementation on fatigue in nonanemic menstruating women with low ferritin: a randomized controlled trial". *CMAJ* 184(2012):1247-1254.
15. Kräyenbühl PA, Battagay E, Breymann C, Furrer J, Schulthess G. "Intravenous iron for the treatment of fatigue in nonanemic, premenopausal women with low serum ferritin concentration". *Blood* 118(2011):3222-3227.
16. Blood donor trial investigators. "The impact of iron supplementation efficiency in female blood donors with a decreased ferritin level and no anaemia: rationale and design of a randomised controlled trial". *BMC Blood Disord* 8(2008):9.
17. Sawada T, Konomi A, Yokoi K. "Iron deficiency without anemia is associated with anger and fatigue in young Japanese women". *Biol Trace Elem Res* 159(2014):22-31.
18. Peuranpää P, Heliovaara-Peippo S, Fraser I, Paavonen J, Hurskainen R. "Effects of anemia and iron deficiency on quality of life in women with heavy menstrual bleeding". *Acta Obstet Gynecol Scand* 93(2014):654-660.
19. FAIR study investigators. "Ferritin screening and iron treatment for maternal anemia and fetal growth restriction prevention: a multicenter randomized controlled trial". *Contemp Clin Trials* 31(2023):101036.
20. Pregnancy trial investigators. "Intravenous ferric derisomaltose versus oral iron for persistent iron deficient pregnant women: a randomised controlled trial". *BMC Pregnancy Childbirth* 23(2023):590.

21. Munro MG, Mast AE, Powers JM, Kouides PA, O'Brien SH, Richards T, et al. "The relationship between heavy menstrual bleeding, iron deficiency, and iron deficiency anemia". *Am J Obstet Gynecol* 229(2023):1-9.
22. Mansour D, Hofmann A, Gemzell-Danielsson K. "A review of clinical guidelines on the management of iron deficiency and iron-deficiency anemia in women with heavy menstrual bleeding". *Adv Ther* 38(2021):201-225.
23. Cook JD, Flowers CH, Skikne BS. "The quantitative assessment of body iron". *Blood* 101(2003):3359-3364.
24. Thurnham DI, McCabe LD, Haldar S, Wieringa FT, Northrop-Clewes CA, McCabe GP. "Adjusting plasma ferritin concentrations to remove the effects of subclinical inflammation in the assessment of iron deficiency: a meta-analysis". *Am J Clin Nutr* 92(2010):546-555.
25. Daru J, Colman K, Stanworth SJ, De La Salle B, Wood EM, Pasricha SR. "Serum ferritin as an indicator of iron status: what do we need to know?". *Am J Clin Nutr* 106(2017):1634S-1639S.
26. World Health Organization. "WHO guideline on use of ferritin concentrations to assess iron status in individuals and populations". World Health Organization, Geneva (2020).
27. Garcia-Casal MN, Pasricha SR, Martinez RX, Lopez-Perez L, Pena-Rosas JP. "Serum or plasma ferritin concentration as an index of iron deficiency and overload". *Cochrane Database Syst Rev* (2021):CD011817.
28. Coad J, Pedley K. "Iron deficiency and iron deficiency anemia in women". *Scand J Clin Lab Invest Suppl* 244(2014):82-89.
29. Fernandez-Gaxiola AC, De-Regil LM. "Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women". *Cochrane Database Syst Rev* (2019):CD009218.
30. Low MSY, Speedy J, Styles CE, De-Regil LM, Pasricha SR. "Daily iron supplementation for improving anaemia, iron status and health in menstruating women". *Cochrane Database Syst Rev* (2016):CD009747.
31. Houston BL, Hurrie D, Graham J, Perija B, Rimmer E, Rabbani R, et al. "Efficacy of iron supplementation on fatigue and physical capacity in non-anaemic iron-deficient adults: a systematic review of randomised controlled trials". *BMJ Open* 8(2018):e019240.
32. Tolkien Z, Stecher L, Mander AP, Pereira DIA, Powell JJ. "Ferrous sulfate supplementation causes significant gastrointestinal side-effects in adults: a systematic review and meta-analysis". *PLoS One* 10(2015):e0117383.
33. Stoffel NU, Cercamondi CI, Brittenham G, Zeder C, Geurts-Moespot AJ, Swinkels DW, et al. "Iron absorption from oral iron supplements given on consecutive versus alternate days". *Lancet Haematol* 4(2017):e524-e533.
34. Auerbach M, Adamson JW. "How we diagnose and treat iron deficiency anemia". *Am J Hematol* 91(2016):31-38.

Citation: Belhadj N, Marchesini C, Timmermans R. "Iron Deficiency Without Anaemia in Menstruating Women: A Case for Screening Before the Haemoglobin Falls." *J Clin Nutr Heal* (2022);3: 001-006