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Original Research Article

Iron deficiency in peri-menopausal women: Clinical considerations from an expert consensus

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ABSTRACT

Background: Iron deficiency (ID) and iron deficiency anaemia (IDA) are usually anticipated to occur during and after pregnancy. Peri-menopausal women are at risk of ID/IDA & warrant attention as the symptoms of ID can be misinterpreted or overlooked. Scientific literatures convey iron deficiency to be considered as a major health problem for perimenopausal women. However, Indian evidence on 'Iron deficiency in peri-menopausal women' is scarce.

Aim: The aim of this article is to understand the impact of iron deficiency on health of peri-menopausal women in India and to understand its important clinical considerations. Developing an expert consensus towards diagnosis & management of iron deficiency and iron deficiency anaemia in this population is the need of the hour.

Materials and Methods: A 3-step modified Delphi method was used to build up the consensus. Nine experts representing gynaecology and endocrinology were invited to participate in the panel discussion. Session was being moderated by a senior gynaecologist. In round 1 – the prevalence of iron deficiency anemia in perimenopausal women and risk factors of iron deficiency anemia were discussed. The panel members asked polling questions and each member's response to the poll question was recorded. The same voting method was used in round 2 and 3, which discussed the diagnosis and management, respectively.

Results: In round 1, round 2 and round 3 statements reached consensus. Consensus was attained for eleven statements representing four different domains: prevalence, risk factors, diagnosis, and treatment.

Conclusion: This consensus guideline will help to standardize care, provide guidance on screening and treatment of iron deficiency anemia in perimenopausal women. This will also assist in clinical decision-making for all healthcare professionals.

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1. Introduction

Anaemia is a common clinical condition with a disproportionate prevalence in women. Globally, it is estimated that 1 of every 4 individuals is anaemic. The prevalence rises to 30% in nonpregnant women and 42% in pregnant women across the world.[1] In United States, according to the United States Centres for Disease Control and Prevention (CDC) data from 1999–2002, anaemia affects almost 7% of reproductive-age women and up to 20% of women > 85 years.[2] Anaemia among perimenopausal women (40-49years) has risen from 47.9% to 54.5%, within the last five years.[3]

Anaemic status, regardless of age of women, has contributed significantly to morbidity and mortality among women and acts as an independent risk factor of clinical concern.[3] Additionally, anaemia in women may be associated with decreased cognitive function, concentration, and attention (in women as their kids)[4,5], lower birth weight in neonates, possible increased risk of preterm delivery; and disturbed postpartum maternal-infant interaction, potentially leading to developmental deficits in childhood.[6]

Anaemia-related quality of life deficits include loss of vitality, fatigue, depression, diminished physical function, and impaired work performance.[7] Restless leg syndrome and pica are specially linked to iron deficiency anaemia. Iron deficiency anaemia can lead to diminished exercise capacity and cold intolerance.[8] Standardized quality of life assessment instruments reveal scores for anaemic women comparable to those of patients with serious chronic diseases of major organ systems. These scores are directly proportional to the severity of anaemia.[7]

The period between 40 and 55 years, which covers pre-menopause (45-50 years), perimenopause (40-49 years), and for some women, post-menopause, has a great impact on women's health and quality of life. This natural life stage lasts 4–11 years and is associated with variations in hormonal levels; menstrual disturbances with an increased risk of heavy bleeding; and an unhealthy lifestyle. With the iron data obtained from the Third National Health and Nutrition Examination Survey (NHANES III), shows that concurrent but inverse changes occur between iron and estrogen levels in healthy women during menopausal transition. Whereas estrogen decreases because of the cessation of ovarian functions, iron increases as a result of decreasing menstrual periods.[9] This is often associated with restrictive dieting and a lack of exercise, and subsequent changes in physical and mental well-being. Fatigue is often experienced as a commonly reported symptom.[1–3] The prevalence of anaemia was found to be 27.8%, and the risk for anaemia was increased among women between 15-49 years of age (2.7 times higher), menstruating (and premenopausal) (2.4 times higher).[10] It is estimated that about 20% of women suffer excessive menstrual blood loss, accounting for 40 of every 1,000 medical consultations annually.[11] Blood loss due to menstruation is a common cause of iron deficiency anaemia (IDA) in perimenopausal women.

Unfortunately, there does not seem to be enough awareness that ID can still be a problem in women of perimenopausal age group, as Symptoms of ID/IDA are nonspecific in nature and can be wrongly interpreted with many differential diagnoses in clinical picture. Despite its wide prevalence and significant consequences, anaemia receives little attention from either the medical community or the public at large.[12]

2. Materials and Methods

This consensus process incorporated a three-step modified Delphi method which included meetings conducted in March 2021. The Delphi method is recommended for use in the healthcare setting as a reliable means of determining consensus for a defined clinical problem. This method is an iterative process that uses a systematic scaling of consequent rounds of voting. Modified Delphi is an effective process for determining expert group consensus where there is little or no definitive evidence and expert opinion playing a crucial role.[13] Initially, a comprehensive list of questions was identified, and consensus was built from the feedback provided by expert participants from the preceding rounds. The modified Delphi method consisted of three rounds of questions in a virtual meet setting. The modified Delphi method was chosen because it allowed for expert interactions in the final rounds. This allowed members of the panel to provide clarification on anaemic problems and further debate to justify their viewpoints. Panel selection of eight experts was taken, since five to ten experts are considered adequate for content validation. Eight experts in the field of gynaecology primarily menopause specialists were initially contacted and asked to participate in consensus development. All eight provided consent for participation via virtual meetings for consensus development. Therefore, experts were chosen to represent professional groups which directly influence patient care and would benefit from clinical practice guidelines. Since the goal of the study was to develop standards of care based on scientific information and medical advice, patients were not included as panel experts. Panel members were identified and selected based on their clinical and research expertise in the evaluation and treatment of patients with iron deficiency anaemia in perimenopausal age group. The panel consisted of endocrinologist and gynaecologist. Once panel members were contacted and consent was obtained, the goals and processes of the project were explained.

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2.1. Round 1

2.1.1. Physical and psychological manifestations

Regarding physical and psychological manifestations in perimenopausal women, literature states that anaemia is prevalent in women of all age groups, including adolescents and reproductive women. However, there are some studies conducted in certain states of India (including Rajasthan, North India & West Bengal) which outpace (range from 78 to 88%) prevalence of iron deficiency in peri-menopausal women. Literature does not define the percentage of Indian perimenopausal women experiencing physical and psychological manifestations. Thus, clinical question based on individual panellist has been put forth to understand the clinical burden of the condition.

2.1.2. Clinical evidence

Literature suggests that perimenopause is associated with significant impact on women's health. Patients often present with erratic menstrual periods, onset of physical symptoms, increased blood levels of FSH, anovulatory cycles and with significant reduction in fertility. In addition, they present with joint aches, loss of bone mineral density and dry skin. During premenopausal period, the monthly blood loss due to menstruation is the major cause of iron deficiency. Transition to menopause i.e., during perimenopause phase, menstrual periods become irregular, with fluctuations lasting up to 10 years until menopause. This can hamper iron stores or levels in the body and can correlate to iron deficiency. However, iron accumulates in the body after menopause because iron is no longer lost through menstruation. Moreover, unhealthy lifestyle & dietary habits pose significant impact on patients' physical and mental well-being and quality of life, which is indirectly linked to iron status. Iron deficiency is associated with several abnormal health functions like cellular dysfunction, mitochondrial dysfunction, abnormal enzyme activity, abnormal transport, modified structural proteins, altered neurotransmitter synthesis and apoptosis. A study by Jagtap BL, et al evaluated psychiatric morbidity in 108 perimenopausal women aged 45–55 years and reported that 44.44% had psychiatric problem.[14]

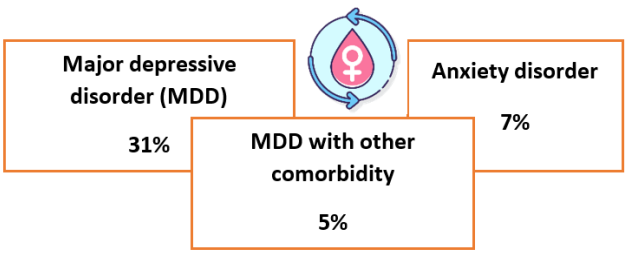


Fig. 1: Psychological problems

Q 1. In your clinical practice, what percentage of perimenopausal women experiences physical and psychological manifestations?

The polling result for this question were as follows:

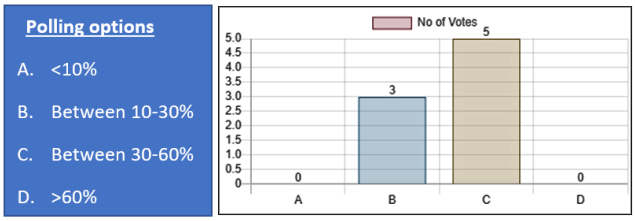


Fig. 2: Polling options and results of question 1

Response: 5 doctors responded incidence to be between 30% to 60%, and 3 doctors responded incidence to be between 10% to 30%.

2.1.3. Consensus statement

Menopausal transition is associated with significant changes in the hormonal parameters. Nowadays, majority of the patients are aware of the symptoms, and they come to seek medical advice. Thus, majority of patients from the peri-menopausal age group present with physical and psychological manifestations (shortened or longer cycles, hot flushes, the sweats and tiredness, heavy bleeding and vaginal dryness, some women also experience emotional and psychological symptoms such as anxiety, irritability, poor concentration, and low self-esteem, which can often be mistaken for depression**.**

2.2. Prevalence of anaemia

Anaemia is the commonest nutritional disorder globally and in India. As per National Family Health Survey (NFHS-4) data from the year 2016, 58.6% of children, 56% of adolescent girls, and 52.4% of pregnant women were found to be anaemic[3]. However, no data has been reported for iron deficiency anaemia in perimenopause women.

2.2.1. Clinical evidence

Nutritional iron deficiency is common in peri-menopausal age group women.Menstrual loss or irregular menstruations puts women at risk of developing iron deficiency or iron-deficiency anaemia. It is essential to manage and treat iron deficiency and iron-deficiency anemia for improved quality of life. Studies analysing prevalence of iron deficiency in perimenopausal age group in India is sparse. A study of approximately 250 postmenopausal woman aged 45 to 80 years conducted in North India the prevalence of anaemia was reported to be 85.2% among postmenopausal women. Another study conducted among 509 postmenopausal women conducted in West Bengal showed the prevalence of mild, moderate, and severe

anaemia among the postmenopausal women was 20.8%, 35.8% and 2.2%, respectively. And a study conducted in Rajasthan among 200 women showed the overall prevalence of anaemia among 45-55year pre- and post-menopausal women was about 83.5 percent having the Haemoglobin level below the much cut off level of 12 recommended by the WHO (1989).[15]

Q 2. In your clinical practice, what is the prevalence of iron deficiency anaemia in perimenopausal women?

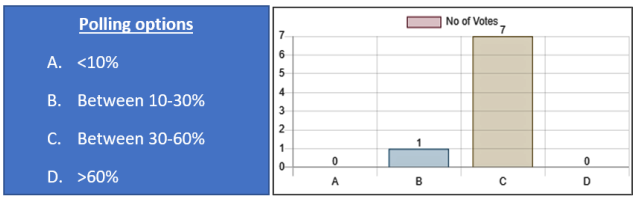


Fig. 3: Polling options and results of question 2

Responses: 7 doctors responded incidence to be between 30% to 60%, and 1 doctor responded incidence to be between 10% to 30%.

2.2.2. *Consensus statement*

Prevalence of iron deficiency anaemia in perimenopausal women is between 30–60%.

2.3. *Iron deficiency anaemia: Risk factors*

Major risk factors for iron deficiency anemia include socio-economic status, nutritional status, hand hygiene and worm infestation, and majority of patients lack awareness. During this pandemic situation of COVID-19, many patients are taking care of their health with favorable nutritional supplements boosting health and immunity. Currently, data are insufficient to support recommendations for or against the use of any vitamin, mineral, herb or other botanical, fatty acid, or other dietary supplement ingredient to prevent or treat COVID-19. And by law, dietary supplements are not allowed to be marketed as a treatment, prevention, or cure for any disease; only drugs can legally make such claims.[15]

2.3.1. *Clinical evidence*

Menstrual disorder like menorrhagia accounts for 5%–10% of the women presenting with IDA in the perimenopausal age group.[16] Heavy menstrual bleeding (HMB) or menorrhagia with blood loss >80 mL, presents in 11 to 13% of the general population and increases with age, reaching 25% in women older than 41 years.[17] HMB is an important cause of anaemia in peri-menopausal women, but it is under detected in women aged 40–55 years.

Q 3 . Is iron deficiency due to gastrointestinal bleeding, the major risk factor in perimenopausal women?

Responses: All 8 doctors responded and agreed that iron deficiency due to gastrointestinal bleeding is the major risk factor in perimenopausal women.

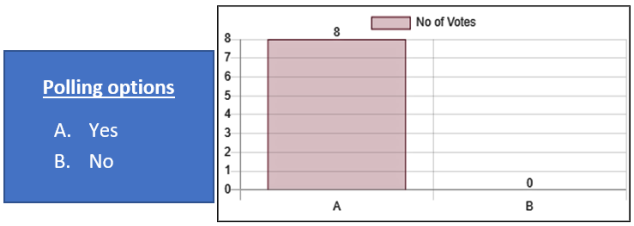


Fig. 4: Polling options and results of question 3

2.3.2. *Consensus statement*

Iron deficiency anaemia due to gastrointestinal bleeding is a major risk factor in perimenopausal women.

2.4. *Round 2*

2.4.1. *Inadequate iron intake*

2.4.2. *Clinical evidence*

Perimenopausal women are at risk of iron deficiency due to low dietary iron intake resulting from restrictive dieting aimed at losing weight. 93% of menstruating women (pre and perimenopause) had dietary iron intakes lower than the recommended dietary allowance (RDA), at approximately 12 mg/day instead of the 18 mg/day recommended. Vegetarians and vegans have a greater risk of ID, owing to heme iron intake being almost nil. Vegetarian diets provide adequate amounts of non-heme iron, based on consumption of wide variety of fruits, cereals, and vegetables.

Q 4. Which of the following factors causes malabsorption of iron that led to iron deficiency in perimenopausal women?

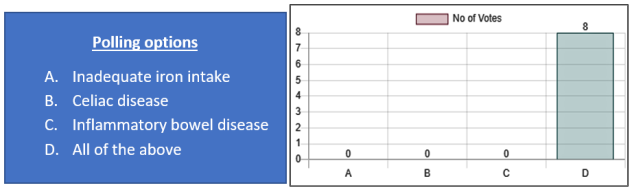


Fig. 5: Polling options and results of question 4

Responses: All 8 doctors responded that inadequate iron intake, celiac disease and inflammatory bowel disease are responsible for malabsorption of iron in perimenopausal women.

2.4.3. *Consensus statement*

Inadequate iron intake, celiac disease and inflammatory bowel disease are responsible for malabsorption of iron in perimenopausal women.

2.4.4. Malabsorption and inflammatory conditions

Iron deficiency is reported in about 80% of anaemic patients with inflammatory diseases due to impaired iron absorption and blood loss. According to the British Society of Gastroenterology guidelines, serological testing for tissue transglutaminase antibody (tTG-IgA) or endomysial antibody (EMA-IgA), and/or duodenal biopsy should be considered in all patients with iron-deficiency anaemia with an aim to screen patients with celiac disease.[18]

Furthermore, inflammation may be responsible for rise in serum ferritin levels, independent of iron status, which may further mask the iron deficiency. Obesity is the chronic inflammatory disorder that may affect iron status, resulting due to inadequate intake of iron.

	Increased risk of iron deficiency
D	Diet: weight loss, vegetarian or vegan diet, low intake of Vitamin C, high intake of tea, Ca^{2+}
E	Excessive sport
F	Fatigue or other symptoms of ID
I	IUD or HMB
C	Celiac disease
I	Inflammatory conditions (IBD, obesity)
T	Anticoagulants, antiplatelet agents, NSAIDs, aspirin or excessive blood donation

Fig. 6: DEFICIT checklist to detect the risk of iron deficiency and iron deficiency anaemia in middle-aged women

Q 5. Chronic inflammatory conditions like obesity can also affect iron stores due to inadequate iron intake or higher body surface area?

Fig. 7: Polling options and results of question 5

Responses: All 8 doctors responded and agreed that obesity has a significant impact on iron stores, resulting due to inadequate iron intake or higher body surface area.

2.4.5. Consensus statement

Most of the obese perimenopausal women present with deficient iron stores to clinics with obesity being a major risk factors leading to iron deficiency.

2.4.6. Clinical evidence

Hepcidin acts as the main regulator of systemic iron and is mainly produced by the liver and concentrations are regulated by body iron status, anaemia, hypoxia, and inflammation. Increased serum levels of hepcidin are associated with reduced dietary iron absorption and decreased systemic iron bioavailability. Hepcidin is markedly increased in obese individuals compared to lean, which imply hepcidin playing an important role in iron depleted obese patients. Women with greater adiposity were unable to improve their iron status by dietary medium as compared to lean controls.[19]

2.5. Clinical assessment of iron deficiency - Role of serum ferritin

Q. 6. Serum ferritin is the most effective clinical marker for the evaluation of iron deficiency

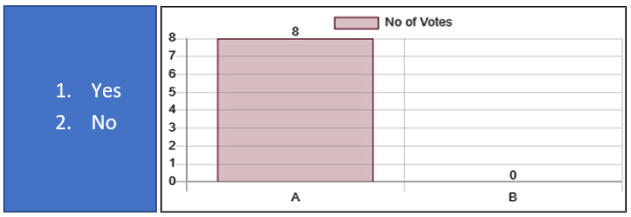


Fig. 8: Polling options and results of question 6

Responses: All 8 doctors responded and agreed that Serum ferritin is the most effective clinical marker for the evaluation of iron deficiency.

2.5.1. Consensus statement

Serum ferritin is a sensitive and doing a complete blood count can also determine whether the patient is suffering from moderate or severe anaemia. Serum ferritin is an acceptable clinical marker to identify iron stores. Thus, its evaluation can be considered important to determine iron deficiency.

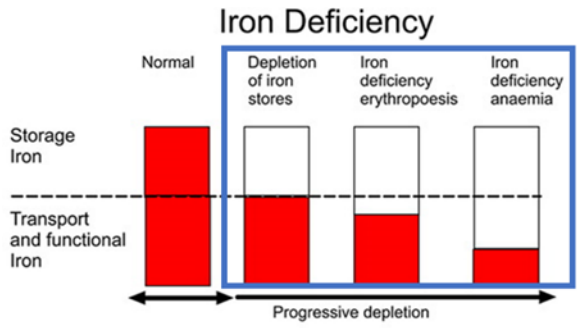
2.6. Pathological importance of iron reserves

2.6.1. Clinical evidence

Identification of iron deficiency before occurrence of iron deficiency anaemia is crucial to receive timely treatment. Fall in serum ferritin denotes impact on iron stores. Measuring inflammatory marker such as C-reactive protein due to presence of any conditions involving inflammation is critical, as it influences iron status. In addition, malignancy, liver disease and alcohol consumption can impact serum ferritin levels.

Ferritin is the primary cellular storage protein for iron and ferritin is low in iron deficiency anaemia. Transferrin levels aid in diagnosis of iron overload rather than iron deficiency. Serum levels of soluble transferrin receptor (sTfR) is increased in iron deficiency anaemia. Also, sTfR:ferritin ratio can be useful for further distinguishing women with elevated ferritin levels due to lack of iron

as opposed to the inflammation associated with chronic disease.



Iron status	Normal	Mild deficiency	Marginal deficiency	Severe deficiency
Haemoglobin	Normal	Normal	Normal	Low
Other Fe functions	Normal	Normal/low	Low	Low
Stores (SF)	Normal	Normal/low	Low	Low

Fig. 9: Iron storage, deficiency, and transport function

Q 7. Analysis of iron overload is crucial for perimenopausal women

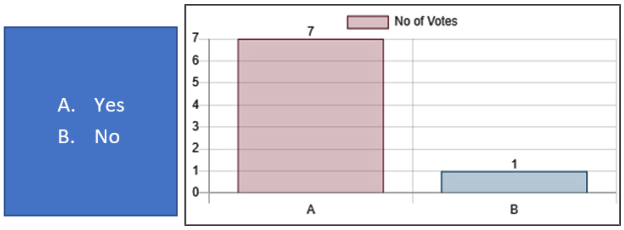


Fig. 10: Polling options and results of question 7

Responses: 7 doctors responded and agreed, and 1 doctor did not agree that analysis of iron overload is important for perimenopausal women.

2.6.2. Clinical evidence

Estrogen decreases by cause of cessation of ovarian functions and iron increases due to decreased menstrual periods. Thus, increased iron can be considered as a risk factor and a complex problem to manage in menopause-related diseases.

A low ferritin value confirms IDA, and an overly high ferritin value is thought to be either due to an associated inflammatory process or unmonitored high iron intake, such as by self-medication with over-the-counter supplements containing iron, or a real iron overload possibly related to genetic factors. Increased iron could lead to oxidative stress and sensitize the skin to UV exposure. Increased iron levels could also boost proliferation of osteoblast progenitors without differentiation to mature osteoblasts and thus,

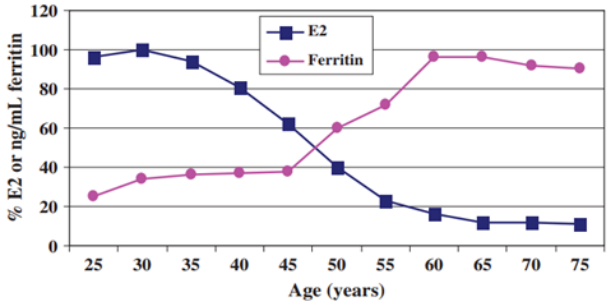


Fig. 11: Inverse changes in iron and estrogen levels during menopause

slow bone formation. In case of hemochromatosis, diet changes and other treatments can help ease the symptoms of hemochromatosis. This can also help prevent or delay further damage to your organs. Your healthcare provider will probably ask you to avoid supplements with iron. You may also need to stay away from foods with too much iron, limit vitamin C and alcohol consumption. Indication of iron chelation therapy removes extra iron from your body.

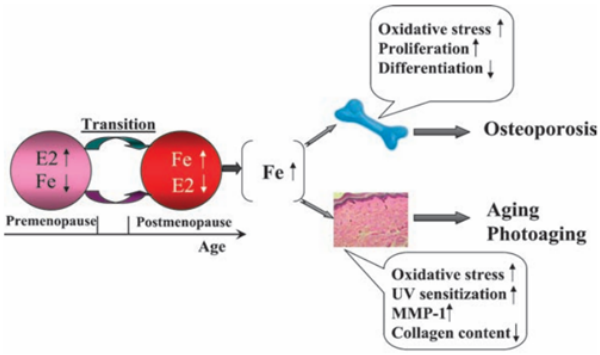


Fig. 12: Clinical implications of iron overload during menopausal period

Q 8. At what serum ferritin levels does cognition and neuropsychological functions are impacted in perimenopausal women?

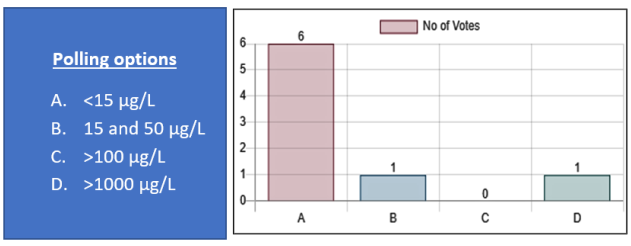


Fig. 13: Polling options and results of question 8

Responses: Serum ferritin levels of <15 μg/L was agreed by 6 doctors, levels between 15 and 50 μg/L were agreed by 1 doctor and 1 doctor mentioned levels of >1000 μg/L can impact neuropsychological functions in perimenopausal women.

2.6.3. Clinical evidence

Correlation of ferritin levels and iron deficiency in perimenopausal women

In adults,

SF: <15 μg/L denotes iron deficiency

1. SF: 15 and 50 μg/L denotes probable iron deficiency
2. SF: 50 and 100 μg/L denotes possible iron deficiency
3. SF: >100 μg/L denotes unlikely to have iron deficiency
4. SF: >1000

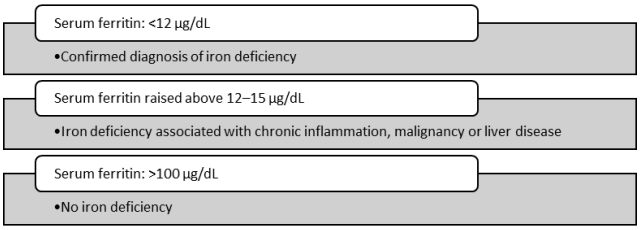


Fig. 14: Implications of serum ferritin levels – Guideline recommendations

2.7. Clinical effects of iron deficiency and poor iron status in perimenopausal and premenopausal women

Iron deficiency in perimenopausal women leads to apathy, irritation, depression, fatigue, or poor cognition. Highest concentrations of iron are found in substantia nigra, deep cerebellar nuclei, the red nucleus, the nucleus accumbens, and portions of the hippocampus.Appropriate levels of brain iron are necessary for optimal brain development and functioning.Iron status has an impact on cognitive performance (including spatial ability, attention, memory, learning, reasoning ability and executive functioning).Peri-menopausal women with iron deficiency have reported to have poorer results on tests of attention, learning and memory when compared to iron sufficient participants.

Q 9. Do you rule out other conditions or factors associated with iron-deficiency anemia in perimenopausal women?

Responses: 8 doctors responded and agreed that it is important to rule out other clinical conditions or factors associated with iron-deficiency anaemia in perimenopausal women.

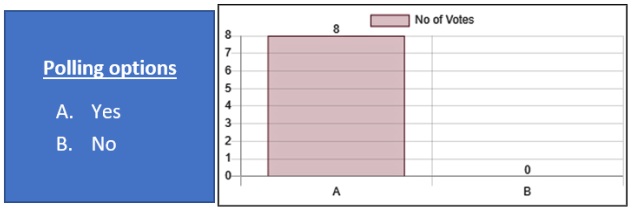


Fig. 15: Polling options and results of question 9

2.7.1. Clinical evidence

Gastrointestinal (GI) diseases and other conditions associated with iron deficiency

Common causes

- NSAID use
- Colonic cancer/polyps
- Gastric cancer
- Angiodysplasia
- Crohn's disease
- Ulcerative colitis

Uncommon causes

- Esophagitis
- Peptic ulcer
- Oesophageal cancer
- Intestinal telangiectasia
- Lymphoma
- Duodenal polyp
- Carcinoma of the ampulla of Vater
- Meckel's diverticulum
- Hookworm

Malabsorption

- Celiac disease
- Gastrectomy
- Gut resection
- Bacterial overgrowth
- Whipple's disease
- Lymphangiecta

Q 10. Does addition of zinc to iron supplementation provide therapeutic response in the management of iron deficiency in premenopausal/menopausal or perimenopausal women?

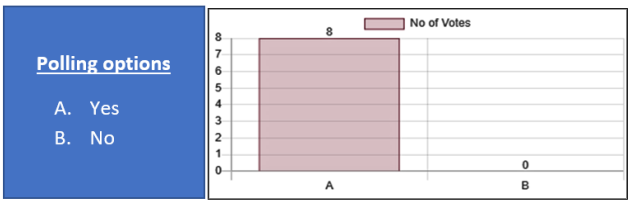


Fig. 16: Polling options and results of question 10

Responses: 8 doctors responded and agreed on zinc and iron supplementation can provide therapeutic response in the management of iron deficiency in premenopausal/menopausal or perimenopausal women.

2.7.2. Clinical evidence

Iron supplementation improves cognitive function regardless of whether the participant suffers from ID or IDA. Iron supplementation is associated with significant improvement in serum ferritin and was linked to five- to seven-fold improvement in cognitive performance. Iron supplementation appeared to improve memory and intellectual ability in women up to age 55 years. Zinc supplementation has reported significant improvement in mood function.

As per Murray-Kolb and Beard,[12] women receiving iron supplementation experienced a significant improvement in serum ferritin and showed significant improvement on measures of attention. Improvement in serum ferritin levels was also associated with significant improvement in learning abilities. Iron supplementations also improved depressive symptoms in iron-deficient women compared to placebo. Supplements containing zinc significantly decreased scores on anger-hostility and depression-dejection scales on the Profile of Mood States (POMS).

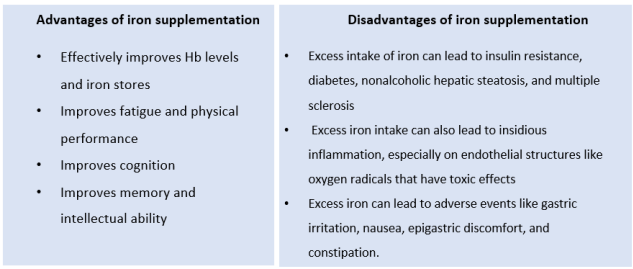


Fig. 17: Therapeutic advantages or disadvantages of iron supplementation in perimenopausal women

3. Conclusion

Iron deficiency can have a major impact on general health and quality of life, hence and is regarded as major health concern for perimenopausal women. Insufficient iron reserves & compromised Hb production can lead to iron-deficiency and iron deficiency anaemia, which further lead to impaired cognitive function and mood status in perimenopausal women. Low iron intake, elevated blood loss due to menorrhagia, IUD device or GI bleeding, malabsorption, obesity, and inflammatory conditions in peri-menopausal women place a patient at risk of iron deficiency. Risk of iron overload should be dealt on priority in perimenopause and postmenopausal women.

It is crucial to assess ID in this patient population, and evaluation of haemoglobin levels can aid in appropriate diagnosis and treatment. Selection of an ideal iron supplement should mainly rely on its effectiveness and minimal GI side effect profile. Hence, considering pathological and physiological status of perimenopausal women, it is important to rebuild iron stores and consider iron supplementation as a valuable therapeutic option for managing iron deficiency and iron deficiency anaemia in perimenopausal population.

4. Source of Funding

Procter & Gamble Health Limited, Mumbai, Maharashtra, India

5. Conflict of Interest

The authors declare no conflict of interest.

Acknowledgments

Exicon Consulting Pvt. Ltd.

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