

Practical Guidance on Managing Iron Deficiency in Women of Childbearing Age - A Saudi Arabian Expert Consensus

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Abstract

Micronutrient deficiencies are a major healthcare problem in the Middle East. Iron deficiency (ID) and iron deficiency anemia (IDA) in particular are common in women of reproductive age. Although prevention and treatment of ID and IDA in women of childbearing age is a public health priority, a lack of clear guidance on diagnosis and management hinders patient care in Saudi Arabia. Therefore, ten experts from Saudi Arabia convened to discuss and draft approaches to screening, diagnosing, and treating women of childbearing age, with the aim of standardizing patient management across the country. Given the similarities across the Middle East, Africa, Asia, and Latin America with respect to healthcare infrastructure and the socioeconomic status of most patients, recommendations stated within this paper have wider applicability.

Keywords: Iron Deficiency; Intravenous Iron; Anemia, Pregnancy; Menorrhagia

Abbreviations

CBC: Complete Blood Count; CDC: Centers for Disease Control and Prevention; Hb: Hemoglobin; Hct: Hematocrit; HMB: Heavy Menstrual Bleeding; ID: Iron Deficiency; IDA: Iron Deficiency Anemia; IV: Intravenous; MCH: Mean Corpuscular Hemoglobin; MCHC: Mean Corpuscular Hemoglobin Concentration; MCV: Mean Corpuscular Volume; NSAID: Nonsteroidal Anti-Inflammatory Drug; RBC: Red Blood Cell; RCT: Randomized Controlled Trials; sTfR: Soluble Transferrin Receptor; TIBC: Total Iron Binding Capacity; TSAT: Transferrin Saturation; WHO: World Health Organization

Introduction

Micronutrient deficiencies are a major healthcare problem in the Middle East, with over one-third of the population being iron deficient or anemic [1]. The prevalence of anemia in Saudi Arabia presents a moderate public health risk according to the World Health Organization (WHO); 32.0% of pregnant women and 32.3% of women of reproductive age are known to have anemia [2]. Data from Saudi Arabia also suggest that the risk of iron deficiency anemia (IDA) increases 3- to 6-fold in women with a menstrual

period duration > 8 days, a history of clots, or heavy bleeding [3]. Additionally, the risk of IDA increases 2- to 4-fold in women with a low intake of meat; and the risk of iron deficiency (ID) increases by 6- to 9-fold in women on nonsteroidal anti-inflammatory drugs and antacids [3].

Despite the lack of data specifically relating to ID and IDA in Saudi Arabia, the prevalence of anemia in pregnant women has been the subject of studies in a number of regions, including Makkah (39.0%) [4], Al-Ahsa (73.3%) [5], Asir region (31.9%) [6] and Al-Khobar (41.3%) [7]. Anemia has been demonstrated to increase in prevalence through pregnancy, with 50.2 - 71.8% of women having anemia in the third trimester [4,7]. Within the Saudi Arabian population, risk factors associated with anemia in pregnant women and women of childbearing age include younger age, more children, less time between pregnancies, low level of education, personal or family history of anemia, low frequency of meat consumption, history of menstrual blood clots, history of menstrual flooding, and use of nonsteroidal anti-inflammatory drugs and antacids [3,4,6,8].

Importantly, ID is the most common cause of anemia, accounting for about 50% of all cases [9] making prevention and treatment of ID a priority, especially in vulnerable groups. There remain several challenges when selecting an appropriate iron replacement product that meets the needs of the patient, and more often than not the pathogenesis of ID continues to be unaddressed and iron repletion remains ineffective [9]. This may be due to inappropriate treatment; for example, a lack of early consideration of intravenous iron therapy.

The prevention and treatment of ID and IDA in women of childbearing age is a public health priority; however, there remains inconsistency and lack of clear guidance on its diagnosis and management in Saudi Arabia. Therefore, ten experts from Saudi Arabia came together to discuss approaches to and establish standards for screening, diagnosing, treating, and monitoring ID and IDA in women of childbearing age. Given that the healthcare infrastructure and the socioeconomic status of the majority of patients are similar across the Middle East, Africa, Asia, and Latin America, recommendations stated within this paper have wider applicability.

Scope of the guidance and approach

A group of nine gynecologists and one hematologist, each with over 15 years of clinical practice experience in Saudi Arabia, met on 20 April 2018 in Dubai, UAE, with the aim of outlining practical guidance on managing ID and IDA in women of childbearing age to establish clinical standards in patient care (Table 1). Consensus was reached through an open discussion covering the need for screening, when and how to screen, confirming a diagnosis, selecting and planning treatment, and monitoring patients. The objectives and clinical questions that were used as a reference for discussion during the consensus meeting were drafted prior to the meeting under guidance and agreement from the expert panel. Clinical questions were built using the PICOTS method [10].

This paper will outline recommendations for managing ID and IDA in women with heavy menstrual bleeding and during pregnancy and the postpartum period. This document is intended for use by local general physicians, women’s healthcare professionals, and gynecologists, for the management of the aforementioned patients. However, physicians are required to manage patients based on the best available evidence and using their clinical judgment, and should also take factors such as patient characteristics, drug profile and available resources into consideration.

A literature review was conducted using PubMed. Articles were searched systematically and only articles in English that were published between January 2000 and February 2018 were extracted. Search terms used were iron deficiency, iron deficiency anemia, heavy menstrual bleeding, pregnancy, postpartum, Saudi Arabia. Articles were short listed based on title and then abstracts

General objectives	
<ul style="list-style-type: none"> To establish standards in screening, diagnosing, treating, and monitoring ID and IDA in women with HMB, during pregnancy, and postpartum, for physicians practicing in Saudi Arabia To improve overall quality of life in women with ID and IDA 	
Patient group	Specific objectives
HMB	<ul style="list-style-type: none"> To prevent anemia and the need for blood transfusion, regardless of the cause of HMB
Antenatal	<ul style="list-style-type: none"> To raise hemoglobin in anemic women, to avoid blood transfusion, and to give prophylaxis to women at risk of bleeding To promote normal development of the fetus To reduce maternal and perinatal morbidity and mortality
Postnatal	<ul style="list-style-type: none"> To improve quality and quantity of breastmilk To reduce the risk of postpartum hypertension, postnatal depression, infection, and sudden death/morbidity

Table 1: General and specific objectives for managing iron deficiency and iron deficiency anemia in women of childbearing age.

Abbreviations: HMB: Heavy Menstrual Bleeding; ID: Iron Deficiency; IDA: Iron Deficiency Anemia.

were reviewed for relevancy. Literature searching was conducted by the medical writers and shared with the experts as reading material prior to the meeting.

Summary of key recommendations

Primary screening tests for ID/IDA

- Complete blood count (CBC) - hemoglobin (Hb), hematocrit, red blood cells, mean corpuscular volume, mean corpuscular Hb, mean corpuscular Hb concentration
- Serum ferritin.

Secondary screening tests for ID/IDA

- Total iron binding capacity
- Soluble transferrin receptor
- Blood film evaluation
- Transferrin saturation (if available).

General dietary advice

- Consume food rich in “heme” iron (See table S1).

Oral iron treatment

- All patients should receive a trial of oral therapy (60 mg elemental iron) for at least 1 month before moving to intravenous iron.

Sources of heme iron ¹	<ul style="list-style-type: none"> Clams, oysters, shrimp, and sardines Organ meats like liver Beef, lamb and duck
Factors affecting iron absorption ^{1,2}	<ul style="list-style-type: none"> Certain foods block iron absorption - coffee, tea, egg yolks, phytates in fiber-containing foods, calcium in milk, and soy protein Acute or chronic inflammation conditions like inflammatory bowel disease, Crohn's disease Certain medications like proton pump inhibitors

Table S1: Foods rich in heme iron and factors interfering with iron absorption.

Sources: 1: *Your guide to anemia. National Heart, Lung, and Blood institute. NIH Publication No. 11-7629. Published September 2011. <https://www.nhlbi.nih.gov/files/docs/public/blood/anemia-yg.pdf>. Accessed September 3, 2018.*

2: *NIH iron factsheet. <https://ods.od.nih.gov/factsheets/Iron-HealthProfessional/?print=1>. Accessed September 3, 2018.*

Intravenous iron treatment

- Intravenous therapy, second line, may be initiated in patients who do not respond or who are poor responders to oral iron.
- Intravenous iron may be initiated as first-line therapy in the following circumstances:
 - Patient is intolerant to oral iron.
 - Patient has undergone gastrointestinal or bariatric surgery.
 - Patient needs a rapid increase in Hb; for example, patient is scheduled for surgery.
 - Hb < 8 g/dL.
- Patients suspected of non-compliance to oral iron or expressing a preference for intravenous iron may be considered for intravenous iron as first-line treatment, at the treating physician's discretion.

Intramuscular iron treatment

- Intramuscular iron treatment is not recommended for the management of ID/IDA because it is painful, associated with gluteal sarcomas, causes permanent discoloration of the skin, and its toxicity has not been shown to be less than that of intravenous iron [11].

Blood transfusion considerations

- Asymptomatic patients with Hb < 5 g/dL may be considered for blood transfusion as first-line therapy.
- Patients at high risk for bleeding, with Hb < 6 g/dL, should be considered for blood transfusion as first-line therapy.

Overview of specific recommendations and evidence summary Patients with heavy menstrual bleeding

Table 2 summarizes the key consensus statements for evaluating, diagnosing, treating, and monitoring ID/IDA in patients with heavy menstrual bleeding (HMB). The diagnosis and treatment algorithm for iron deficiency/iron deficiency anemia for patients with heavy menstrual bleeding is shown in figure 1 (for IV iron dosing refer to figure S1 and figure S2).

1.1	HMB can be diagnosed by asking the patient about: <ol style="list-style-type: none"> Number of sanitary towels or tampons used Extend of soaking Passage of clots Leakage Prolonged or frequent menstruation and Impact of menstruation on social life and daily activities.
1.2	A thorough patient history of every patient with HMB suspected of ID or IDA should include details on history of anemia, ID, or IDA; history of oral or intravenous iron use; medication use, especially anticoagulant and NSAID use; and history of bariatric surgery.
1.3	Women with HMB presenting with symptoms of fatigue, dizziness, palpitations, hair fall, lack of concentration (especially for working women), psychological distress (depression, nightmares, restless leg syndrome), and pica should be suspected of ID/IDA.
1.4	All women with HMB suspected of ID or IDA should undergo a complete blood count and serum ferritin test (primary screening tests).
1.4.1	Anemia should be strongly suspected in patients with low Hb, Hct, RBC, MCV, MCH, MCHC.
1.4.2	ID should be strongly suspected in patients with low RBC, MCV, MCH, MCHC.
1.4.3	ID and IDA can be confirmed if patients have serum ferritin < 30 ng/mL.
1.5	If serum ferritin levels are normal, ID and IDA may be confirmed in patients with TIBC < 240 µg/dL, hypochromic blood film, and serum sTfR < 2 mg/L (secondary screening tests).
1.6	If serum ferritin levels are abnormally high, ID and IDA can be confirmed in patients with TSAT < 20%.
1.6.1	TSAT is a good indicator of ID even before it develops; however, given that TSAT is not commonly available and is expensive in Saudi Arabia, a hematologist may be consulted to reach a definitive diagnosis of ID or IDA.

1.7	All women who are non-symptomatic but at high risk of developing ID or IDA should receive oral iron as prophylaxis.
1.8	All women with a confirmed diagnosis of ID/IDA should receive oral iron supplements containing 60 mg elemental iron for a period of 1 month as first-line treatment.
1.8.1	Oral iron should be supplemented alone and not combined with any other treatment.
1.8.2	Oral iron should be taken 30 minutes prior to food or 2 hours after food to increase bioavailability of iron.
1.8.3	Antacids reduce iron absorption and should not be taken prior to oral iron supplement.
1.8.4	No more than one tablet containing 60 mg of elemental iron should be dosed per day for a period of 1 month.
1.8.5	A trial intermittent dosing regimen may be initiated in women that are intolerant to oral iron before considering intravenous iron.
1.9	Determining response to iron therapy.
1.9.1	Women with a 1% increase in reticulocyte count and an improvement in Hb by 0.5 g/dL after 30 days are considered responders and should be continued on oral iron for 2 more months.
1.9.2	At 3 months, if Hb does not increase by 2 g/dL, the patient is considered a poor responder, or suspected of being non-compliant, and should be switched to intravenous iron.
1.9.3	At 3 months, if Hb increases but serum ferritin < 30 ng/mL, patient should be considered a non-responder and switched to intravenous iron.
1.10	Intravenous iron may be initiated in patients that are not responding to, poor responders to, or intolerant to oral iron.
1.10.1	Intravenous iron dose may be calculated using the formula: [Target Hb - current Hb] × weight in kg × 4 = intravenous iron dose.
1.10.2	If intravenous iron sucrose is selected, ≤200 mg of intravenous iron sucrose should be dosed per day.
1.11	Intravenous iron may be initiated as first-line treatment in women that have undergone gastrointestinal surgery; require a rapid rise in Hb due to imminent surgery; or are at high risk of bleeding. Intravenous iron may be considered as first-line treatment in women expressing a preference for it.

1.12	Blood transfusion may be considered as first-line treatment in (i) asymptomatic patients with Hb < 5 g/dL and (ii) symptomatic patients with Hb < 6 g/dL.
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Table 2: Consensus statements for the management of iron deficiency/iron deficiency anemia in patients with heavy menstrual bleeding.

Abbreviations: Hb: Hemoglobin; Hct: Hematocrit; HMB: Heavy Menstrual Bleeding; ID: Iron Deficiency; IDA: Iron deficiency anemia; MCH: mean corpuscular hemoglobin; MCHC: Mean Corpuscular Hemoglobin Concentration; MCV: Mean Corpuscular Volume; NSAID: Nonsteroidal Anti-Inflammatory Drug; RBC: Red Blood Cell; sTfR: Soluble Transferrin Receptor; TSAT: Transferrin Saturation.

Summary of evidence

ID and IDA are underestimated, underdiagnosed, and undertreated in women with HMB in Saudi Arabia. In clinical practice, it has been commonly observed that those women with HMB that do receive treatment for ID/IDA are often treated inappropriately.

Clinical evaluation

HMB can be defined as the loss of ≥ 80 mL menstrual blood during menstruation. HMB can also be defined in terms of frequency of sanitary towel or tampon change, menstrual flooding, use of more than one sanitary product type simultaneously, or the presence of large blood clots in menses. HMB affects women’s quality of life, with reports of moderate or severe pain and interference with everyday life activities [12]. HMB can result in fatigue [13], ID and anemia [14] and lead to losses of 5 - 6 times more iron than that experienced by women with normal blood loss during menstruation [15] which increases the risk of ID.

Underlying causes of HMB

HMB can result from ovarian cysts, fibroids, and bleeding disorders, among other causes. Genetic polymorphisms have also been implicated in risk of HMB and anemia [16]. Diagnosis of the condition can be subjective, and accurate quantification of menstrual blood loss can be an expensive undertaking [17]. Although ascertaining the underlying cause of HMB is important, the screening, diagnosis, and treatment of the causes of HMB are outside the scope of this paper. The implementation of systems to define and manage abnormal uterine bleeding in women, such as the International Federation of Gynecology and Obstetrics systems, will help guide and tailor treatment options [18].

Investigations and diagnosis of ID and IDA

Prior to prescribing iron supplementation, it is of paramount importance that iron status is assessed appropriately [9]. CBC assessment is used as a standard of care to screen for anemia in

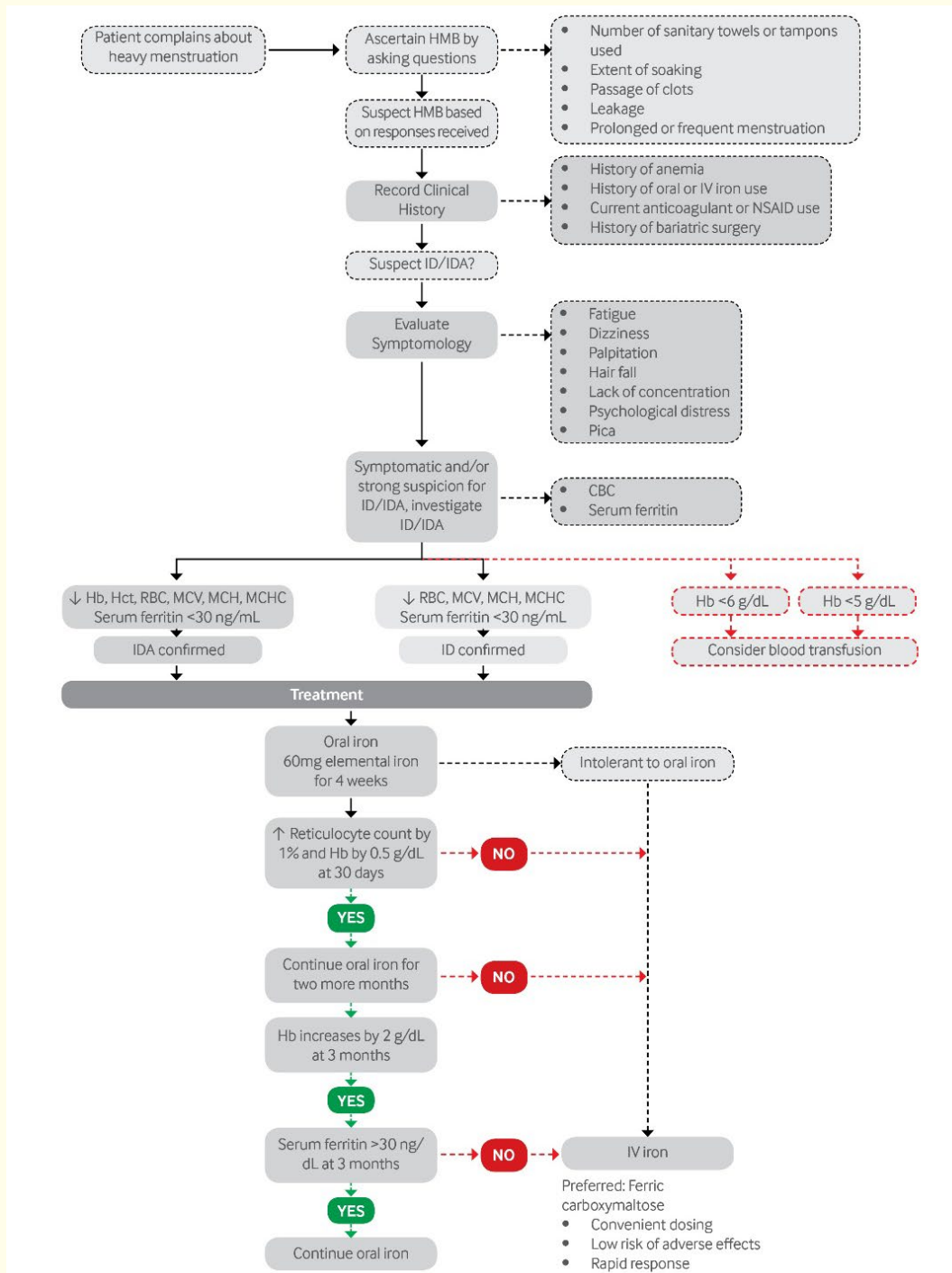


Figure 1: Diagnosis and treatment algorithm for iron deficiency/iron deficiency anemia for patients with heavy menstrual bleeding.

Abbreviations: CBC: Complete Blood Count; Hb: Hemoglobin; Hct: Hematocrit; HMB: Heavy Menstrual Bleeding; ID: Iron Deficiency; IDA: Iron Deficiency Anemia; IV: Intravenous; MCH: Mean Corpuscular Hemoglobin; MCHC: Mean Corpuscular Hemoglobin Concentration; MCV: Mean Corpuscular Volume; RBC: Red Blood Cell.

women of childbearing age. Although Hb < 12 g/dL through a CBC assessment may be useful to detect anemia, the diagnosis of ID requires further evaluation.

Hb and blood counts are often insufficient methods for detecting iron deficiency in women with HMB, whereas the serum ferritin test enables its diagnosis and early treatment [19]. Serum ferritin is the most frequently used laboratory test for evaluating iron stores,

Ferric Carboxymaltose | Abbreviated Dosing Guide

Determining iron need

Hb (g/dL)	Patient body weight		
g/dL	<35 kg	35 to <70 kg	≥75 kg
<10	500 mg	1500 mg	2000 mg
10 to <14	500 mg	1000 mg	1500 mg
≥14	500 mg	500 mg	500 mg

Do not administer ferric carboxymaltose

- if patient is allergic (hypersensitive) to the product or any of the other ingredients of this medicine
- if patient has experienced serious allergic (hypersensitive) reactions to other injectable iron preparations
- if patient has anaemia not caused by iron deficiency
- if patient has an iron overload (too much iron in your body) or disturbances in the utilisation of iron

INTRAVENOUS INFUSION

- Once a week
- Up to 20 mL of FCM = 1000 mg of iron
- Sodium chloride solution for dilution, volume up to 250 mL (brown solution)

Maximum single dose 20 mg iron/kg body weight, should not exceed 1000 mg iron

Dilution plan

Volume of FCM required	Equivalent iron dose	Max amount of sterile 0.9% m/V sodium chloride solution	Minimum administration time
2 to 4 mL	100 to 200 mg	50 mL	No minimal time
>4 to 10 mL	>200 to 500 mg	100 mL	6 mins
>10 to 20 mL	>500 to 1000 mg	250 mL	15 mins

Do not administer subcutaneously or intramuscularly

Observe for adverse effects for at least 30 mins after each dosing session

Patient monitoring

- Re-assessment should be performed by the clinician based on the individual patient's condition.
- The Hb level should be re-assessed no earlier than 4 weeks post final FCM administration to allow adequate time for erythropoiesis and iron utilisation.
- In the event the patient requires further iron repletion, the iron need should be recalculated using the above Table to determine iron need.
- Oral iron therapy should not be started for at least 5 days after the last injection of FCM, as FCM may reduce oral iron absorption.

COMMON (may affect 1 in 10 patients)

Headache
 Dizziness
 Flushing
 High BP
 Nausea
 Injection site reactions

SERIOUS (requires immediate attention)

Hypersensitivity reactions

Refer to full prescription information for further details

Source, Ferinject 50 mg iron/mL solution for injection/infusion. Patient information leaflet. Approved by Saudi Food and Drug Authority. This leaflet was last approved in version number: 02/2017

Figure S1: Ferric carboxymaltose dosing information.

with a serum ferritin level of < 30 ng/mL having a sensitivity of 92% and specificity of 98% for the identification of absolute ID, with or without anemia [9]. Although a normal serum ferritin level (30 - 300 ng/mL) excludes the presence of ID, it is important to note that ferritin is an acute-phase reactant and its levels are profoundly

affected by inflammation [9]. In the presence of inflammation (for example, C-reactive protein > 5 mg/L) and transferrin saturation < 20%, serum ferritin levels between 30 and 100 ng/mL suggest absolute ID, whereas ferritin > 100 ng/mL usually indicates iron sequestration, commonly seen in anemia of chronic inflammation [9].

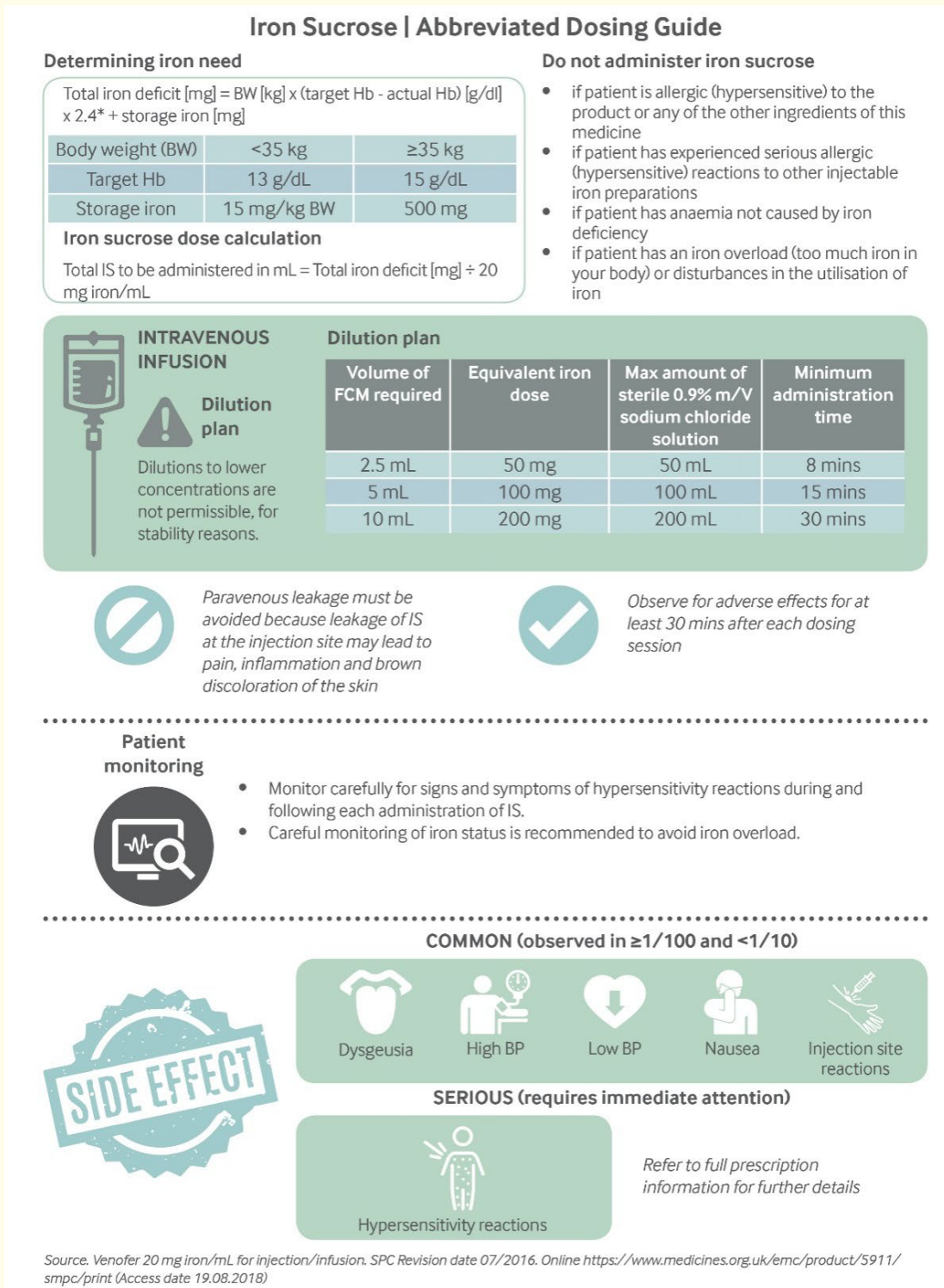


Figure S2: Iron sucrose dosing information.

Physiologically, as iron stores reduce, red cells become microcytic, determined by mean corpuscular volume < 80 μL, and then hypochromic, determined by mean corpuscular Hb < 28 pg [9].

Additionally, in patients with ID, higher red cell distribution width (> 15 μm) and thrombocytosis have been observed [9]. Patients with ID also show microcytosis, hypochromia, anisocytosis, and poikilocytosis on a peripheral blood smear [9].

Treatment

In women with HMB, defined as the loss of ≥ 80 mL blood during menstruation, the average yearly blood loss approximates to about 1L, which is equivalent to 1 - 1.5g of iron lost [20]. Studies also indicate that women with HMB have a high requirement for blood transfusions and are known to have lower quality of life and higher hospital costs than women with normal blood loss [20]. Although iron supplementation is necessary to prevent the need for blood transfusions in women with HMB, oral iron is unlikely to keep pace with iron loss [20].

Although oral iron replacement therapy is the mainstay of treatment for IDA, it is poorly tolerated and may be ineffective [21]. An analysis of five randomized controlled trials (RCTs) comparing oral versus intravenous iron therapy for IDA concluded that at day 14, if the change in Hb level is < 1.0 g/dL with oral iron, a transition to intravenous iron should be considered [21]. However, change in Hb level of ≥ 1.0 g/dL on day 14 was predictive of a satisfactory overall Hb response to oral iron on day 42/56 (positive and negative predictive values of 92.9% and 72.7%, respectively), with high sensitivity (90.1%) and specificity (79.3%) [21].

Ferrous sulfate is the most common treatment choice for women with HMB and IDA [22]. However, two RCTs have demonstrated intravenous iron formulations to be more effective than oral iron in restoring levels of Hb and iron stores in the form of ferritin [23,24]. In the first study, which included 76 patients with Hb < 9 g/dL scheduled to undergo surgery due to menorrhagia, 76.7% of patients on intravenous iron sucrose (3 weeks before surgery) were reported to achieve their target Hb compared with 11.5% of patients randomized to receive oral iron protein succinylate (80 mg/day) [23]. Additionally, intravenous iron sucrose achieved significantly higher Hb (3.0 vs. 0.8 g/dL; *P* < 0.0001) and ferritin levels (170.1 vs. 4.1 µg/L; *P* < 0.0001) than oral iron protein succinylate [23]. The second study, in 477 women with HMB and IDA, reported that more patients assigned to ferric carboxymaltose than oral ferrous sulfate had Hb ≥ 2 g/dL (82% vs. 62%, respectively, *P* < 0.001), Hb ≥ 3 g/dL (53% vs. 36%, respectively, *P* < 0.001) and Hb ≥ 12 g/dL (73% vs. 50%, respectively, *P* < 0.001) at 6 weeks [24]. In addition, women on ferric carboxymaltose reported better vitality and physical function, and improved fatigue (*P* < 0.05), versus oral iron [24]. Furthermore, two recent reviews of ferric carboxymaltose have also highlighted its importance in correcting iron stores in women with HMB [25,26] its superior tolerance to oral iron (ferrous sulfate) [25] and its potential to provide cost savings from a payer perspective [26].

Following the restoration of Hb levels to within normal range, treatment usually continues for a further 3 months to allow iron stores to be replenished [27]. Treatment of both HMB and IDA has been associated with improved quality of life [28].

Antenatal patients

Table 3 summarizes the key consensus statements for evaluating, diagnosing, treating, and monitoring ID/IDA during the antenatal period. The diagnosis and treatment algorithm for iron deficiency/iron deficiency anemia during the antenatal period is shown in figure 2 (for IV iron dosing refer to figure S1 and figure S2).

2.1	Women with symptoms of depression and heightened/ aggravated pregnancy symptoms should be suspected of ID/IDA.
2.2	A thorough medical history of every pregnant woman should include details on risk factors for ID or IDA such as socioeconomic class; anticoagulant use; history of bariatric surgery; short inter-pregnancy interval; multiple gestation pregnancy; abnormal placentation; history of antepartum hemorrhage; history of anemia; and history of blood transfusion.
2.3	All pregnant women undergo CBC assessment as a part of the first antenatal evaluation, which is repeated every 3 months and at the time of delivery, as part of standard antenatal care.
2.3.1	Women with Hb < 11 g/dL are diagnosed with anemia.
2.3.2	Women with Hb < 11 g/dL should undergo serum ferritin evaluation.
2.3.3	Women with serum ferritin < 30 ng/mL are diagnosed with ID.
2.3.4	Women with Hb < 11 g/dL and serum ferritin < 30 ng/mL are diagnosed with IDA.
2.3.5	CBC may be evaluated before the next scheduled 3-monthly visit if the patient is symptomatic.
2.4	If serum ferritin levels are normal, ID and IDA may be confirmed in patients with TIBC < 240 µg/dL, hypochromic blood film, and serum sTfR < 2 mg/L.
2.5	If serum ferritin levels are high, ID and IDA can be confirmed in patients with TSAT < 20%.
2.5.1	TSAT is a good indicator of ID even before it develops; however, given that TSAT is not available throughout Saudi Arabia and is expensive, a hematologist may be consulted to reach a definitive diagnosis of ID or IDA.
2.6	Caution is advised when recommending liver consumption, especially during the first trimester, as this may potentiate nausea and/or vomiting.
2.7	All pregnant women should receive oral iron as prophylaxis, regardless of hematological parameters.

2.7.1	Pregnant women on prophylactic oral iron who are intolerant or have nausea or vomiting during the first trimester may be started on intermittent iron supplementation.
2.7.2	It is recommended to reiterate the need to be compliant with oral iron at all antenatal visits.
2.8	All pregnant women in the first and second trimester with a confirmed diagnosis of anemia and/or ID/IDA should receive oral iron supplements containing 60 mg elemental iron for a period of 1 month as first-line treatment.
2.8.1	Oral iron should be supplemented alone and not combined with any other treatment.
2.8.2	Oral iron should be taken 30 minutes prior to food or 2 hours after food to increase the bioavailability of iron.
2.8.3	Antacids reduce iron absorption and should not be taken prior to oral iron supplement.
2.8.4	No more than one tablet containing 60 mg of elemental iron should be dosed per day.
2.8.5	A trial intermittent dosing regimen (1 to 3 days apart) may be initiated before changing the type of oral iron or considering intravenous iron in women that are intolerant to oral iron.
2.9	Determining response to iron therapy.
2.9.1	If Hb does not increase by 2 g/dL after 4 weeks of oral iron treatment, the patient is considered a non-responder and should be switched to intravenous iron, except during the first trimester.
2.9.2	During the first trimester of pregnancy, women with ID/IDA not responding to oral iron may be referred to a hematologist for investigation, at the discretion of the treating physician.
2.10	Intravenous iron is contraindicated in pregnant women at < 14 weeks' gestation.
2.11	Intravenous iron may be initiated in patients that are not responding to, poor responders to, or intolerant to oral iron.
2.11.1	Intravenous iron dose may be calculated using the formula: [Target Hb - current Hb] × weight in kg × 4 = intravenous iron dose.
2.11.2	If intravenous iron sucrose is selected, ≤ 200 mg should be dosed per day.
2.12	Intravenous iron may be initiated as first-line treatment in pregnant women at at least 32 weeks of gestation, with Hb < 10 g/dL, irrespective of risk profile.

2.13	In the third trimester, intravenous iron may be considered in high-risk patients or those with an anticipated risk of bleeding, at the discretion of the treating physician.
2.13.1	Anemic women electing for a cesarean section or those with placenta previa are at a high risk of bleeding and should be pre-emptively given intravenous iron to compensate for inadvertent blood loss.
2.14	Although it is rare, if pregnant women are intolerant to intravenous iron they should be referred to a hematologist for further evaluation.
2.15	Blood transfusion may be considered first-line in (i) asymptomatic patients with Hb < 5 g/dL, and (ii) symptomatic patients at high risk of bleeding with Hb < 6 g/dL.
2.15.1	Before blood is transfused to a pregnant woman, cross-matching is essential to ensure compatibility of blood.

Table 3: Consensus statements for the management of iron deficiency/iron deficiency anemia during the antenatal period.

Abbreviations: CBC: Complete Blood Count; Hb: Hemoglobin; ID: Iron Deficiency; IDA: Iron Deficiency Anemia; sTfR: Soluble Transferrin Receptor; TIBC: Total Iron Binding Capacity; TSAT: Transferrin Saturation.

Summary of evidence

Clinical evaluation

IDA in pregnancy is caused by two main factors. First, an increase in maternal plasma volume during pregnancy leads to hemodilution of circulating cells, including red blood cells [29]: Hb concentration can decrease by 1 - 2 g/dL by the second trimester [30]. Second, the body requires approximately 1000 mg more iron overall during pregnancy: 350 mg for growth of the placenta and fetus, 500 mg associated with increased red blood cell mass in the mother, and 250 mg for delivery-associated blood loss [31]. This translates to a gradual increase in iron requirement from 0.8 mg per day in the first trimester to 7.5 mg per day in the third trimester [32]. To meet this increased iron requirement during pregnancy, the body consumes iron stores, increasing the risk of ID and IDA [31].

Physiologically, anemia during pregnancy reflects the expansion of plasma volume by 50% relative to the increase in RBC mass by 25% [32]. More importantly, ID is the most common cause of anemia during pregnancy, due to maternal-fetal transfer of iron, which potentiates a decrease in maternal iron reserves [32].

Anemia in pregnancy can have implications for both fetus and mother. Maternal mortality has been shown to increase in cases of

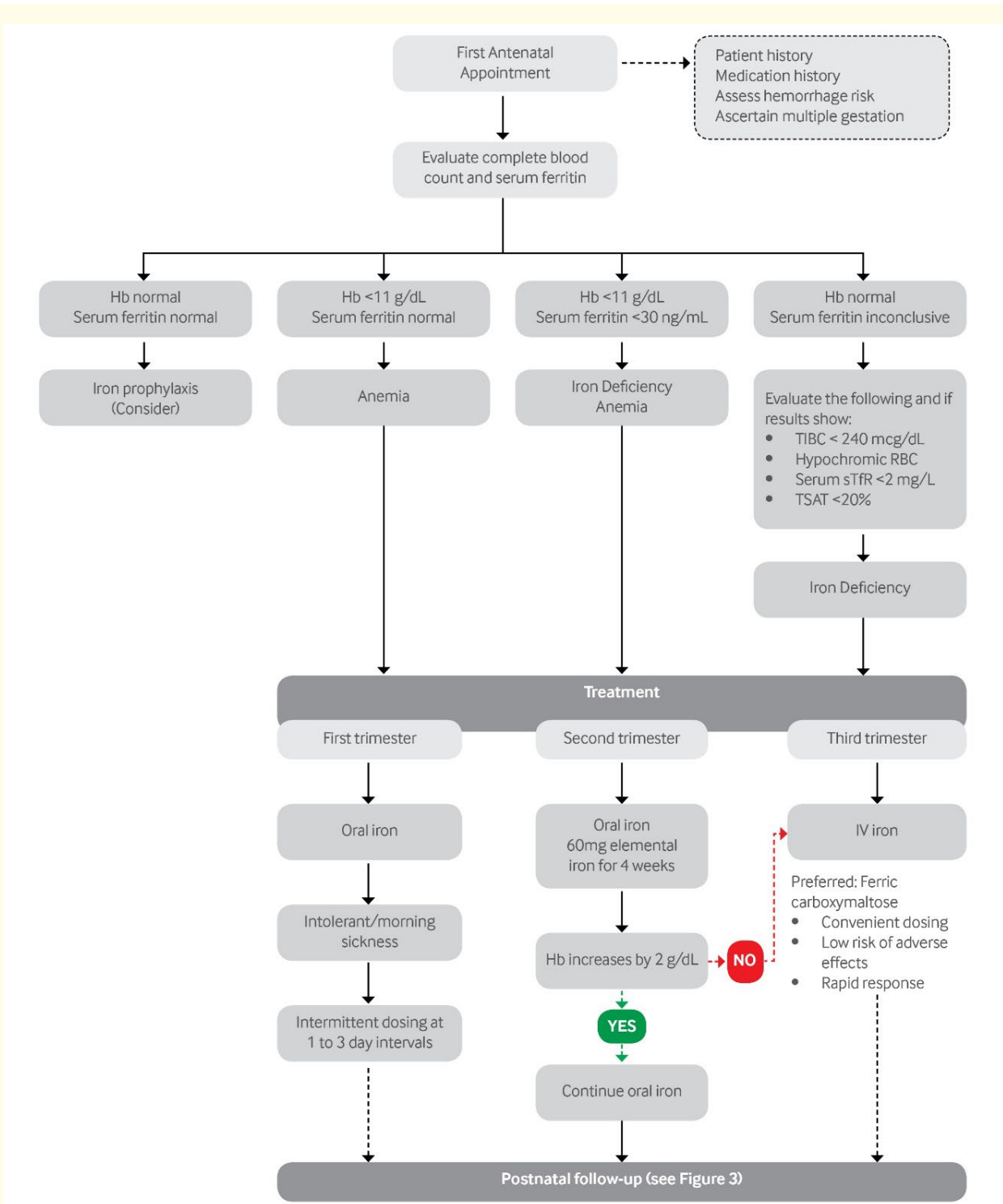


Figure 2: Diagnosis and treatment algorithm for iron deficiency/iron deficiency anemia during the antenatal period.

moderate (relative risk = 1.35; 95% confidence interval (CI): 0.92 - 2.00) and severe (relative risk = 3.51; 95% CI: 2.05 - 6.00) anemia [33]. Iron deficiency is also associated with maternal morbidity, including immunity and susceptibility to infection [34], stress and depression [35]. Maternal anemia can lead to an increased risk of

preterm birth, low birthweight, and babies small for gestational age, as well as perinatal and neonatal death [36]. Maternal IDA can also increase the risk of IDA in the newborn child [37], affecting neurodevelopment [38], auditory recognition memory [39] and mental development [40].

The prevalence of anemia and IDA are 14 - 52% and 12 - 17%, respectively, in pregnant women who have not received iron supplementation [41]. Despite this, iron deficiency screening for women of childbearing age across Saudi Arabia is not yet optimized.

Investigations and diagnosis of ID and IDA

Anemia in pregnancy is defined as Hb < 11 g/dL in the first and third trimesters and Hb < 10.5 g/dL in the second trimester, according to the Centers for Disease Control and Prevention (CDC) [42]. ID is most commonly defined as serum ferritin < 30 ng/mL [43].

Pregnancy often leads to significant physiological changes, which influence laboratory values [44]. For example, lower hematocrit and Hb concentrations are normal during pregnancy, whereas a serum creatinine level of 1.1 mg/dL is recognized as abnormal during pregnancy [44]. It is therefore important to consider reference ranges specific to pregnancy when interpreting some laboratory results [44].

Treatment

Guidance regarding which foods enable adequate uptake and absorption of iron in pregnancy is provided by countries including the United Kingdom and Norway [41]. However, most (80%) pregnant women do not achieve the minimum recommended iron uptake via diet alone [45] as the average daily absorption of iron from Western diets is about 1 - 5 mg [32]. To meet physiological iron demands during pregnancy, there is a need to support higher maternal iron intake, which should increase from 6 mg/day in the first trimester to 19 mg/day in the second trimester, then 22 mg/day in the third trimester [31].

Oral iron is commonly the first choice for IDA prevention in the first two trimesters of pregnancy, taken daily for approximately 2 to 3 months until adequate iron stores have been achieved [32]. Preventive iron supplementation was found to reduce the risk of maternal anemia at term by 70%, IDA by 67%, and ID by 57% [46]. Although daily oral iron reduces the risk of maternal anemia and ID during pregnancy, outcomes are heterogeneous depending on the population risk of low birthweight and anemia, and adherence to treatment [46]. Furthermore, oral iron treatment is associated with significant gastrointestinal side effects (nausea, constipation, diarrhea, indigestion, and metallic taste) in up to 70% of patients, reducing adherence to treatment [32,47]. The high potential for lack of adherence to daily oral iron due to side effects, interrupted supplementation, and concerns about safety in women with adequate iron intake have limited the use of such a dosing regimen in clinical practice [48]. In contrast, intermittent iron supplementation is associated with fewer side effects and a reduced risk of high

level of Hb in mid and late pregnancy, compared with routine iron supplementation, albeit with an increase in risk of mild anemia near term [48]. Therefore, intermittent supplementation may be a feasible alternative for non-anemic pregnant women receiving adequate antenatal care [48].

Given that IDA during the first two trimesters of pregnancy is associated with a 2-fold increased risk of preterm delivery and 3-fold increased risk of delivering a low-birthweight baby, both the CDC [50] and WHO [49] recommend routine iron supplementation of all pregnant women. Oral iron therapy is indicated for mild IDA (hemorrhagic anemia), whereas intravenous iron therapy is indicated for moderately severe to severe anemia (defined as Hb < 9 g/dL) [43]. It is important to note that there is little evidence for the benefits of routine iron supplementation, especially in developed countries, with outcomes being similar when decisions regarding supplementation are made on an individual basis [50,51].

Intravenous iron offers a more rapid rise in both Hb levels and serum ferritin than oral iron formulations [52] and is therefore favored where the patient is intolerant of or non-responsive to oral iron treatment or for pregnant women presenting with IDA late in pregnancy [32].

The risk of allergic/anaphylactic reactions associated with iron dextran has limited its use in pregnancy [53]. However, new-generation parenteral iron formulations permit safe administration of relatively high-dose iron in a single treatment [53,54]. Intravenous iron preparations, ferric carboxymaltose, iron polymaltose, and iron sucrose have been shown to produce similar increases in Hb levels; however, a slightly higher rate of adverse reactions was observed with iron polymaltose [55]. All intravenous iron preparations were found to result in a median increase in Hb of 2 g/dL after 3 - 4 weeks and of 3 g/dL by delivery [55]. However, safety reasons mean that ferric carboxymaltose is the preferred option when intravenous iron therapy is indicated in pregnancy or postpartum [43,55].

Ferric carboxymaltose has been extensively studied in pregnant women. A head-to-head study comparing ferric carboxymaltose (1000 - 1500 mg iron) and ferrous sulfate (200 mg iron/day) for 12 weeks in pregnant women with IDA reported an improvement in Hb levels within a shorter time frame for the ferric carboxymaltose (median 3.4 vs. 4.3 weeks), making it a more appropriate option, especially in the third trimester of pregnancy [56]. Ferric carboxymaltose also improved vitality and social functioning prior to delivery and was associated with fewer adverse events than ferrous sulfate [56]. Another study reported that ferric carboxymaltose increased Hb as early as 3 weeks post

infusion, and mean serum ferritin from 17 µg/L at booking to 151 µg/L post infusion [57]. In pregnant woman at 34 weeks’ gestation, ferric carboxymaltose also increased median Hb from 8.4 g/dL at first administration to 10.7 g/dL at the time of delivery, as reported by a retrospective analysis [58].

The decision to perform a blood transfusion in a pregnant woman with IDA is usually taken on an individual basis, based on severity of symptoms [59] or for a complicated obstetric condition such as a woman with Hb < 9 g/dL undergoing a cesarean section for placenta previa.

Postnatal patients

Table 4 summarizes the key consensus statements for evaluating, diagnosing, treating, and monitoring postnatal patients with ID/IDA. The diagnosis and treatment algorithm for iron deficiency/iron deficiency anemia during the postnatal period is shown in figure 3 (for IV iron dosing refer to figure S1 and figure S2).

3.1	CBC should be evaluated immediately postpartum in all women to screen for ID/IDA.
3.1.1	CBC is not required in women with normal admission hemoglobin.
3.1.2	CBC should be reassessed during the routine postnatal appointment at 6 weeks in: (1) Women that have been anemic during pregnancy (2) Women fulfilling the criteria of postpartum depression (3) Women with a history of pre-pregnancy anemia (4) Women with postpartum hemorrhage, and (5) Women that are symptomatic
3.2	No secondary investigations are recommended during the postnatal period.
3.3	Dietary and treatment recommendations outlined for women with heavy menstrual bleeding should be used as a reference for managing women during the postnatal period.
3.4	All women should be referred to the antenatal clinic for discharge advice and follow-up.

Table 4: Consensus statements for the management of postnatal patients with iron deficiency/iron deficiency anemia.

Abbreviations: CBC: Complete Blood Count; ID: Iron Deficiency; IDA: Iron Deficiency Anemia.

Summary of evidence

Clinical evaluation

Postpartum anemia often results from excessive bleeding during labor or from ongoing ID that begins in pregnancy [60]. Women can experience blood losses of up to 500 mL during vaginal delivery [61] and cesarean-section delivery has been shown to lead to an increased risk of postpartum anemia [62] with greater blood losses of up to 1100 mL during delivery [61]. Further risk factors for

postpartum bleeding, which can in turn lead to maternal anemia, include higher maternal age, low-lying placenta, and multiple pregnancy [61].

Determining the burden of postpartum anemia is limited by rapid discharge of mothers following delivery and the lack of awareness of the condition in many countries [63]. During the first week postpartum, the prevalence of anemia (Hb < 11 g/dL) is 14% in iron-supplemented and 24% in non-supplemented healthy women [60]. The prevalence of anemia in women 6 months after delivery in the United Kingdom is approximately 30% [64]. The prevalence of postpartum anemia, IDA and ID in women in the United States at 0 - 6 months postpartum are estimated to be 10.3%, 4.2%, and 12.7%, respectively [65]. Anemia at 6 months after delivery has been shown to occur in 21.3% of women with normal Hb levels in the third trimester [66].

Postpartum anemia is a significant health problem that can impact on a woman’s quality of life, including cognitive function and emotions [60]. Postnatal depression has also been shown to be associated with anemia in the postpartum period, with a mean Center for Epidemiological Studies-Depressive Symptomatology Scale score of 16.4 in women with Hb ≤ 12 g/dL versus 6.90 in women with Hb > 12 g/dL, 28 days after delivery [67].

Investigations and diagnosis of ID and IDA

Postpartum anemia can be defined as Hb < 10 g/dL at 24 to 48 hours post-delivery [68], < 11 g/dL 1 week after delivery [60] and < 12 g/dL 8 weeks after delivery [60].

Treatment

Ideally, prevention of postpartum IDA should commence during pregnancy to ensure that Hb levels are within a normal range and iron stores are replenished prior to delivery [69]. Following delivery, women without risk factors for postpartum anemia are generally advised to discontinue iron supplementation [42]. Screening at 4 - 6 weeks postpartum is essential to identify anemic women requiring iron supplementation [66]. Diagnosis of postpartum IDA via the measurement of mean corpuscular volume and reticulocyte Hb content, in addition to Hb levels, has been shown to be highly reliable [70].

Oral iron therapy is indicated for mild IDA, whereas intravenous iron therapy is indicated for moderate to severe anemia, defined as Hb < 9 g/dL [43]. Furthermore, patients with IDA on oral iron with a Hb response of < 1 g/dL at day 14 should be transitioned to intravenous iron [21]. This is because increased Hb ≥ 1 g/dL on day 14 was found to accurately predict satisfactory overall Hb response to oral iron on day 42/56, with a sensitivity of 90% and specificity of 79% (positive and negative predictive values of 92.9% and 72.7%, respectively) [21].

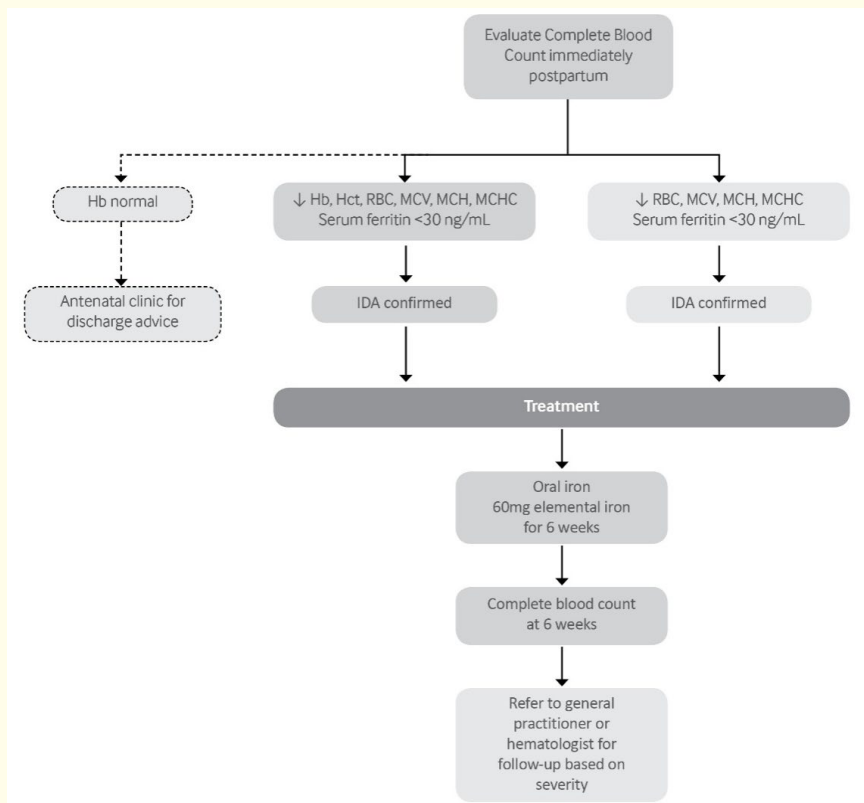


Figure 3: Diagnosis and treatment algorithm for iron deficiency/iron deficiency anemia during the postnatal period. Abbreviations: Hb: Hemoglobin; Hct: Hematocrit; ID: Iron Deficiency; IDA: Iron Deficiency Anemia; MCH: Mean Corpuscular Hemoglobin; MCHC: Mean Corpuscular Hemoglobin Concentration; MCV: Mean Corpuscular Volume; RBC: Red Blood Cell.

Intravenous iron following postpartum bleeding has been shown to improve iron levels, as well as patient-reported fatigue and depression, compared with oral iron treatment [71]. An RCT has also demonstrated greater efficacy of parenteral ferrous sucrose in enhancing ferritin and Hb levels compared with oral ferrous sulfate in women with postpartum IDA [72]. Parenteral iron carboxymaltose had similar efficacy to parenteral iron sucrose in this patient group, despite having a shorter treatment period [73]. Additionally, rapid administration of high-dose ferric carboxymaltose was found to be better tolerated than iron sucrose (overall adverse event rate of 5% vs. 6%, respectively) and was associated with higher compliance [73].

Conclusion

We have identified three vulnerable groups of women in their reproductive age to Iron Deficiency and Iron Deficiency Anemia, namely Heavy Menstrual Bleeding, Antenatal, and Postnatal women. Screening methods along with timely intervention with the appropriate treatment in each group is outlined according to international standards and with specific consideration of applicability to our region.

Conflict of Interest

Each author received travel expenses and an honorarium for participating in the consensus meeting, sponsored by Vifor. Hisham Arab has received speaker honoraria from Bayer, Abbott, and MSD, and advisor honoraria from Vifor and Sanofi. AbdulkareemAlmomen has received speaker honoraria from Pfizer, Novo Nordisk, Novartis, Roche, and Bayer, and advisor honoraria from Pfizer, Novartis, Novo Nordisk, Roche, Sanofi, Bayer, and Vifor. Faisal A. Khashgari has received speaker honoraria from Bayer and advisor honoraria from Bayer and Abbott. Muna A. Al Ghamdi has received speaker honoraria from Sanofi and Vifor, and advisor honoraria from Bayer and Sanofi. Yasir Katib has received speaker honoraria from Sanofi. Abdulrahim Gari, Nabeel Salem Bondagji, Mamoun M. Elawad, Wesam Kurdi and Maysoon bin Obaid have no conflicts of interest to declare.

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Hisham Arab was involved in the conception and execution of the project and helped outline and draft the manuscript. All authors provided critical comments and concepts during the consensus meeting that was incorporated into the manuscript. All authors conducted literature review in support of the recommendations; participated in the consensus meeting for generating recommendations; and contributed to the development, review, and finalization of the manuscript. All authors approved the submitted version of the manuscript.

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