



# Pathophysiology and management of iron deficiency anaemia in pregnancy: a review

J. P. Akshay Kirthan<sup>1</sup> · Manjunath S. Somannavar<sup>1</sup>

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## Abstract

According to World Health Organization (WHO), iron deficiency anaemia (IDA) is considered the most prevalent nutritional deficiency worldwide, affecting approximately 30% of the global population. While gastrointestinal bleeding and menstruation in women are the primary causes of IDA, insufficient dietary iron intake and reduced iron absorption contribute to the condition. The aim of IDA treatment is to restore iron stores and normalise haemoglobin levels in affected patients. Iron plays a critical role in various cellular mechanisms, including oxygen delivery, electron transport, and enzymatic activity. During pregnancy, the mother's blood volume increases, and the growing foetus requires a significant increase in iron. Iron deficiency during pregnancy is associated with adverse outcomes such as maternal illness, low birth weight, preterm birth, and intrauterine growth restriction. Iron supplementation is commonly used to treat IDA; however, not all patients benefit from this therapy due to factors such as low compliance and ineffectiveness. In the past, IV iron therapy was underutilised due to its unfavourable and occasionally unsafe side effects. Nevertheless, the development of new type II and III iron complexes has improved compliance, tolerability, efficacy, and safety profiles. This article aims to provide an updated overview of the diagnosis and management of IDA during pregnancy. It will discuss the advantages and limitations of oral versus intravenous iron and the pathophysiology, diagnosis, treatment, and overall management of IDA in pregnancy.

**Keywords** Iron deficiency anaemia · Treatment · Diagnosis · Pregnancy · Oral iron · IV iron

## Introduction

The WHO states that 30% of women between the ages of 15 and 49 and 37% of pregnant women suffer from iron deficiency anaemia [1]. Children and women are more likely to be affected by iron deficiency anaemia (IDA), but adult men of any age can develop the condition depending on their health and socioeconomic status [2]. Iron deficiency anaemia (IDA) is common among women, where gastrointestinal (GI) bleeding and menstruation are being the common causes; the condition can also be brought on by not

consuming enough iron or an inability to absorb it from the food that one consumes [3].

The National Family Health Survey-5 reports that 45.7 and 54.3% of pregnant women in India's urban areas and rural areas respectively are anaemic [4]. Globally, IDA is directly responsible for 20% of maternal deaths and 50% of foeto-maternal problems. Depending on mother's iron reserve at conception and the body's ability to absorb the iron from the food, it can lead to pregnancy-related iron deficiency.

Women in poor countries often get anaemia while they are pregnant. This means that their iron stores are often not enough and that the changes in their bodies caused by pregnancy are not enough to meet the growing needs. Iron supplements have become commonly used and standard treatment during pregnancy to prevent iron deficiency anaemia [5]. In this review, the iron absorption and distribution, Lab markers for diagnosis of IDA, treatment, and the management of IDA will be discussed. In addition, limitations are identified and improvement recommendations will be made [5].

✉ J. P. Akshay Kirthan  
akshay.kirthan.jp@gmail.com

Manjunath S. Somannavar  
manjunathsomannavar@gmail.com

<sup>1</sup> Department of Biochemistry, JN Medical College, KLE Academy of Higher Education and Research, Nehru Nagar, Belgaum 590010, Karnataka, India

## Pathophysiology

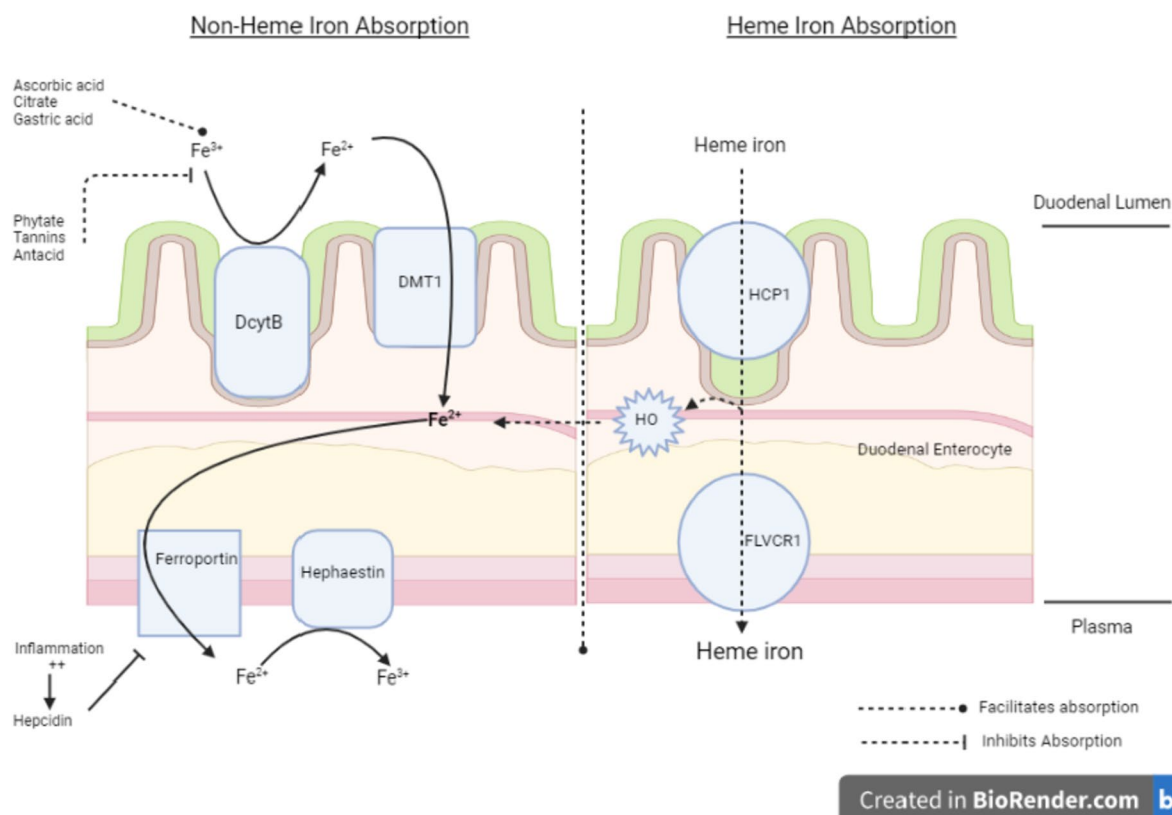
Iron is a necessary element whose levels are mostly controlled by food, intestinal absorption, and iron recycling [6]. There are two different forms of dietary iron: haem and non-haem iron (Fig. 1) [7]. The haemoglobin (Hb) and myoglobin found in meat from animals, poultry, and fish are the sources of haem iron, which is easily absorbed. The haem-carrier-protein (HCP1) delivers haem iron straight into the intestinal cells in the haem absorption pathway. Once inside the enterocyte, the haemoglobin exporter FLVCR1 can either release haem iron into the plasma or turn it back into  $\text{Fe}^{2+}$  using the haemoglobin oxidase (HO) enzyme. The plasma  $\text{Fe}^{2+}$  is then released by the ferroportin receptor. Non-haem-iron is mostly seen in plant foods, which is not absorbed easily. Non-haem-iron absorption is inhibited by natural substances such as phytate, oxalate, polyphenols, and tannin as well as by some drugs like proton pump inhibitors [8, 9]. Gastric acid, citrate, and ascorbic acid, however, enhance iron absorption [10].

The enzyme duodenal cytochrome B (DcytB) transforms the insoluble ferric iron ( $\text{Fe}^{3+}$ ) in the non-haem absorption route into the absorbable ferrous iron ( $\text{Fe}^{2+}$ ).  $\text{Fe}^{2+}$  is transported into the cell via the divalent metal

transporter 1 (DMT1) across the apical surface, where it can be stored as ferritin or released back into the bloodstream by ferroportin. Hephaestin or ceruloplasmin must turn  $\text{Fe}^{2+}$  back into  $\text{Fe}^{3+}$  before it can leave the enterocyte. Hepcidin is a peptide hormone made in the liver. It regulates ferroportin, by making the iron to move into the cell. Plasma iron levels and stores control how much hepcidin is produced and how it moves through the body. Hepcidin levels go up when there is inflammation, which speeds up the breakdown of ferroportin and makes it harder for cells to release iron into the blood. Body requires about 8–18 mg/day of iron, and during pregnancy, it is about 27 mg/day. However, 1–2 mg is only absorbed by the body mostly in the intestinal part of duodenum and proximal jejunum [10].

## Metabolism of iron in pregnancy

In pregnancy, transportation of iron from mother's plasma to baby is controlled by foetal hepcidin. When the hepcidin amount is low, iron gets into the plasma more quickly. When hepcidin levels are high, the body takes in ferroportin. The minimum daily need for iron from outside the body



**Fig. 1** Iron absorption pathways (figure taken and modified with permission from Kumar and Brookes) [7]

continues to range between 1 and 8 mg. But the body needs more iron from outside sources to keep up with its increasing physiological needs during growth, pregnancy, and breastfeeding. During pregnancy, the mother's blood volume increases dramatically, and a large amount of iron is needed to support the growing baby and placenta. Moreover, the expectant women lose iron before and after childbirth [11, 12]. Approximately 1000 mg of iron is lost throughout pregnancy and lactation. Eight milligrams is advised for women who are not pregnant, whereas pregnant women are advised to consume 27 mg of iron per day. In breastfeeding mothers, a daily dietary intake of 10 mg is required [13].

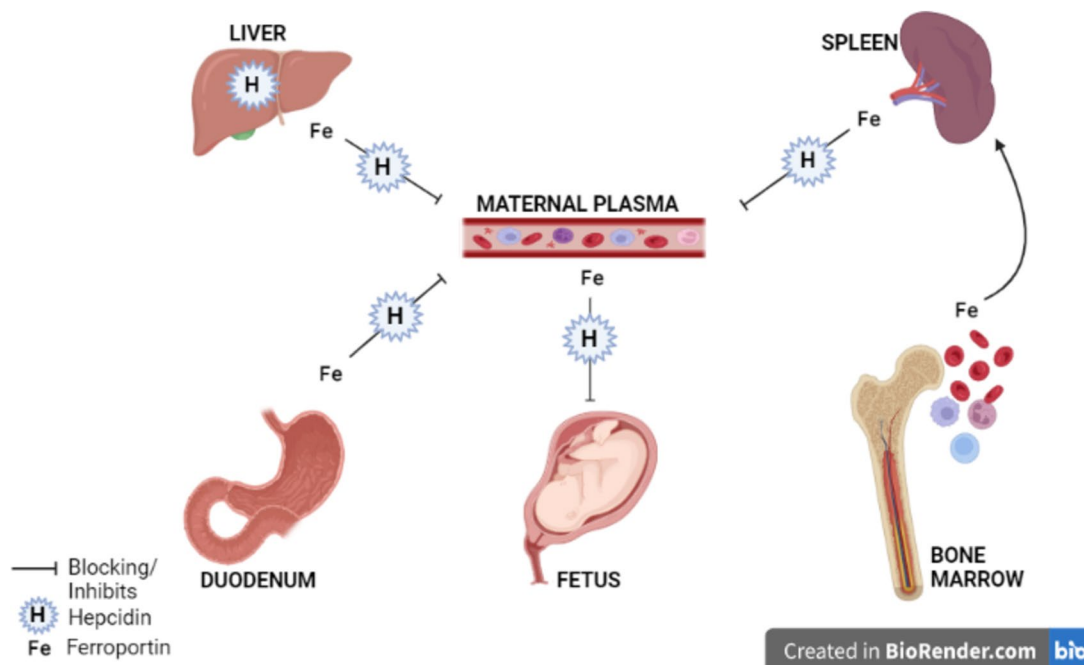
### Physiology of serum iron distribution

Red blood cells (RBCs) are responsible for carrying oxygen, which is done by the protein haemoglobin (Hb). RBCs also carry carbon dioxide to the lungs so that waste products from oxygen use can be released. During pregnancy, a woman's plasma volume goes up by 50%, reaching a peak between 28 and 36 weeks of pregnancy [14]. RBCs, on the other hand, increase by 15 to 25% to carry more oxygen and eliminate the metabolic by-products through the placenta. In pregnancy, physiologic haemodilution is caused by the difference between the increase in plasma volume and the rise in RBCs. Anaemia complicates maternal and foetal oxygen

transfer, whereas normal haemodilution can maintain appropriate placental perfusion by increased cardiac output.

RBCs are constantly made in the bone marrow, and around 2 million RBCs are sent through the bloodstream every minute. RBCs have a lifespan of about 120 days, after which macrophages in the spleen and liver break them down into haem and globin. As a result of the degradation of the globin chain and haem molecule, amino acids, iron, and bilirubin are formed respectively, where bilirubin forms a waste product. The iron is then sent to the hepatocytes of the liver to be stored or sent back into the bloodstream which is then utilised with vitamin B12 during erythropoiesis to make new RBCs.

Two hormones, ferroportin and hepcidin, play a significant part in iron distribution and regulation (Fig. 2). Ferroportin hormone aids in transporting iron stores from intestine, degraded RBCs, and hepatocytes into the bloodstream [15, 16]. Hepatocytes produce hepcidin. When blood iron levels are high, it binds to ferroportin and stops iron from being absorbed [16]. When there is too much iron in the blood, the liver makes more hepcidin. When there is not enough iron in the blood, the liver makes less hepcidin. In this way, the amount of iron in the blood is kept in balance by storing iron in tissues and producing erythrocytes. Serum hepcidin is also involved in how the body responds to an infection, so inflammation can change serum hepcidin levels [17]. Inflammatory events such as preeclampsia and malaria have the potential to modify hepcidin levels and lead



**Fig. 2** Iron distribution and regulation by hepcidin and ferroportin (figure taken and modified from Fisher and Nemeth) [15]

to iron restrictions. When diagnosing anaemia and deciding how to treat each person, it is important to take into account all clinical factors that could be causing it.

During the second and third trimesters of pregnancy, the mother's hepcidin level is lowered so that the placenta can get more iron. The precise mechanism underlying this suppression is not well understood. Concerns about iron overload during pregnancy have been raised as a result of using iron supplements, which may have negative effects on foetal development. However, more recent studies show that maternal hepcidin still facilitates in regulating the level of iron that is readily available for placental uptake in spite of prenatal suppression, shielding the foetus from iron overload [18]. It was found that the placenta stores iron for the foetus to use when there is a serious lack of iron. Therefore, taking iron supplements during pregnancy may result in higher hepcidin levels and less iron available for absorption by the mother [15]. More investigation is required for better understanding of regulatory link between maternal iron deficit, foetal hepcidin, placental iron utilisation, and the effects of iron supplementation during pregnancy.

## Laboratory markers for iron status and diagnosis

Various clinical guidelines state that anaemia during pregnancy is typically defined as Hb less than 11 g/dL or 11.5 g/dL, depending on the gestational age of pregnancy, with a small variation. But if a pregnant woman's haemoglobin level is below 10 g/dL at any time, she should be checked and treated for anaemia, because it could have terrible effects on both the mother and foetus, such as increased risk of intrauterine growth retardation and premature birth. Hb less than 12 g/dL, or less than 11.5 g/dL in some studies, is a temporary cutoff point for anaemia in females of reproductive age [19, 20].

In isolated iron deficiency anaemia, the iron storage molecule known as serum ferritin should be below 30 µg/L [21]. But ferritin is an acute phase protein, and when there is inflammation [22], the amount of ferritin can rise. It is therefore suggestive of IDA if there are concurrent symptoms of inflammation, such as an elevated CRP level and a serum ferritin level less than 100 µg/L [23]. Transferrin is a protein that moves iron around the body. It is usually high, but it can be either normal or low in chronic inflammatory conditions as it is a negative phase protein [24]. IDA can only be diagnosed if TSAT is less than 20% and serum iron is being lower [21].

Table 1 shows the diagnostic criteria for “iron deficiency anaemia”. It should be noted that iron shortage cannot be ruled out because Hb levels are within normal

**Table 1** Diagnostic criteria for iron deficiency anaemia

Iron markers	Diagnosis for IDA
Haemoglobin (Hb)	< 13 g/dL (males) < 12 g/dL (females) < 11 g/dL (pregnant women)
Serum ferritin*	< 30 µg/L (if there is no inflammation) < 100 µg/L (if there is inflammation)
Serum transferrin**	Increased
Total iron binding capacity (TIBC)	Increased
Serum iron	Decreased
Transferrin saturation	Less than 20%
Mean corpuscular volume (MCV)	Low

\*Acute phase protein (positive) which is raised in inflammatory conditions

\*\*Acute phase protein (negative) which can be normal or reduced in inflammatory conditions

ranges, since significant iron loss precedes detectable decreases in haemoglobin. So, a mild iron deficiency without anaemia is shown by a low mean corpuscular Hb (MCH) and a normal Hb or a rise in the red cell distribution width (RDW) [25].

The majority of patients still find it impractical and invasive to have a bone marrow examination, despite the fact that it is the most effective way to diagnose iron deficiency. Serum test analysis is still the most common way to find out if someone has an iron deficiency or anaemia. The most important diagnostic lab test is the complete blood count (CBC), used to figure out how severe and what kind of anaemia a person has at first.

The level of anaemia is measured by Hb and haematocrit. The MCV, MCH, and MCHC concentrations are used to measure the amount of the RBCs. These markers can help find microcytic or macrocytic anaemia, such as thalassemia or folate deficiency or B12 deficiency, respectively [14]. Even if there is no anaemia at the time of the lab test, serum ferritin or TSAT can be added to the complete blood count to find out how much iron is stored and how likely it is that anaemia will happen later in the pregnancy [26, 27].

A precise method for IDA diagnosis involves measuring serum ferritin and soluble transferrin receptors. Nevertheless, most laboratories across the world cannot reliably reproduce the transferrin receptor testing procedure [28]. Serum iron, serum transferrin, TIBC, transferrin saturation, and ferritin are the most common laboratory tests used to find out a person's iron status [29]. It is believed that soluble transferrin receptor (sTfR), which is seen in human plasma and reflects tissue iron deficiency by existing as a transferrin-receptor complex, is a shorter form of the tissue receptor.

Hepcidin is another protein that is important for iron absorption. It is produced by liver cells and then released into the bloodstream. It is a small molecule with a structure made up of 25 amino acids and peptides. It is also produced by the kidneys and can be found and tested in urine [20]. It is a protein that circulates in the plasma ferroportin and responds to various stimuli in order to regulate serum iron levels and storage of iron [30].

### Current approach to evaluate iron deficiency during pregnancy

A complete blood count and MCV are excellent tests for screening for IDA because they can show if someone has microcytic anaemia. In regions of the globe where haemoglobinopathies are prevalent and related with microcytosis, iron studies, specifically ferritin levels, continue to be a relative marker for IDA [31]. When ferritin level is less than 30 g/L, it is called severe iron deficiency (ID), and it is called mild-to-moderate iron deficiency (ID) when the ferritin level is between 100 and 30 g/L. The average range for ferritin is between 20 and 464, and it depends on the lab and the method. In cases where ferritin is higher than 100 g/L and anaemia is also present, a common reactive cause like an infection should be diagnosed. Other causes of anaemia should be investigated afterwards. More iron-related tests, such as serum iron, TIBC, and TSAT, can be tested to determine if IDA is present [32].

The amount of iron stored in the liver is shown by the level of ferritin. Iron deficiency is identified when there is low amount of serum ferritin which often comes before the onset of anaemia. Iron and many other micronutrients are procured predominantly through diet before pregnancy. People who live below the poverty line are more likely to suffer from micronutrient deficiencies because they lack access to sufficient nutritional sources. Teichman et al. found that nutritional access was not the only difference between high-income and low-income households but ferritin value was also significantly different. According to the findings, economically backward people are unlikely to have prenatal screenings for iron storage deficit, which slows down the detection and treatment of iron deficiency and the onset of anaemia [27].

Additionally, due to chronic infection and inflammatory conditions, they may unintentionally increase ferritin levels during pregnancy which are used to detect anaemia due to iron shortage. Due to the fact that persistent infections and inflammation have a smaller impact on TSAT levels in these kind of circumstances, TSAT is a better and more reliable measure of iron storage [33, 34]. Clinicians should be aware

that rheumatoid arthritis, thyroid disorder, and any other inflammation that is often caused by obesity can falsely raise ferritin levels notably during acute episodes or when conditions are poorly controlled [16, 33].

Bó et al. found that the reticulocyte haemoglobin (Ret-Hb) has the potential to be an outstanding alternative tool for the diagnosis of iron deficiency in pregnant women, particularly during prenatal care. Integrating periodic observations of Ret-Hb values into routine blood counts may facilitate tracking for the early onset of anaemia, where a progressive decline in Ret-Hb values may indicate the need for further investigation using conventional iron dosages [35]. Another study identified a Ret-Hb cutoff value of 21.2 pg (sensitivity of 100% and specificity of 64.1%), below which IDA can be predicted. They considered a sensitivity of 100% in order to use the parameter as a screening value for IDA. They concluded that further sensitive and potent parameters are required for the early detection of iron deficiency anaemia [36].

### Intravenous (IV) and oral iron therapy in pregnancy

Studies reported that intravenous iron is more effective than oral iron supplemented alone or given in combination with intravenous iron based on haemoglobin levels [37]. A greater risk of thrombosis has been linked to an IV iron sucrose dosage. In contrast, five daily doses of IV sucrose given over the course of 3 weeks in six small dosages to pregnant women did not cause any infusion-related thrombosis and were tolerated well.

A study reported that there was no significant difference in Hb levels between IV sucrose and ferrous sulphate given at any time tested on 8, 15, 21, and 30 days and at delivery. In contrast, there was a substantial difference in favour of the IV iron sucrose group in a second experiment when Hb levels were measured at 2 and 4 weeks and at delivery using six tiny doses of iron sucrose. However, IV iron sucrose administration needed hospital visits for six infusions in both experiments, as well as increased demands on hospital resources [38].

The data showed that 7.9% of pregnant women who received oral iron tablets had less than usual ferritin levels at the time of delivery when compared to IV iron which had 4.5% less than normal. 29% of pregnant women who consumed oral iron tablets had haemoglobin levels below 116 g/L, compared to 16% of those who received IV iron. In spite of having high frequency and overall burden of iron deficiency anaemia, a meta-analysis revealed that there was a lack of high-quality trials inscribing maternal and perinatal outcomes in women with IDA.



## Adverse effects of IV iron

IV iron was only seldom utilised in the past due to its unfavourable and occasionally severe adverse effects. Recent advances, however, have led to the creation of novel iron complexes of types II and III that are better and more acceptable and being used to replace older formulations to maintain iron reserves quickly. Even though there is more and more proof that the newer intravenous iron preparations are safe for both pregnant women and others in need, intravenous iron is still not used as much as it could be because people used to be concerned about the older IV iron preparations [39].

A review conducted on 481 male and female patients, who underwent iron dextran infusions, showed that approximately 25% of the patients experienced mild side effects which resolved on their own. However, around 2% of individuals encountered severe allergic reactions, with 0.6% of these cases being classified as anaphylactic. Notably, a considerable number of these reactions occurred immediately during the test dose infusion [28]. In contrast, iron gluconate has been reported to have a lower reaction rate, with only 3.3% of allergic reactions per million doses per year. Consequently, a test dose is not recommended for iron gluconate. Furthermore, no life-threatening side effects were associated with the infusion of iron gluconate. Conversely, iron dextran was linked to 31 fatalities and 196 instances of allergic/anaphylactic reactions.

Iron dextran's use during pregnancy is limited due to its frequent adverse reactions, including serious events. Although it is believed that administering iron gluconate is safe, patient compliance and limited healthcare resources make the numerous infusions impractical, rendering it unfeasible in practice [40].

## Adverse effects of oral iron

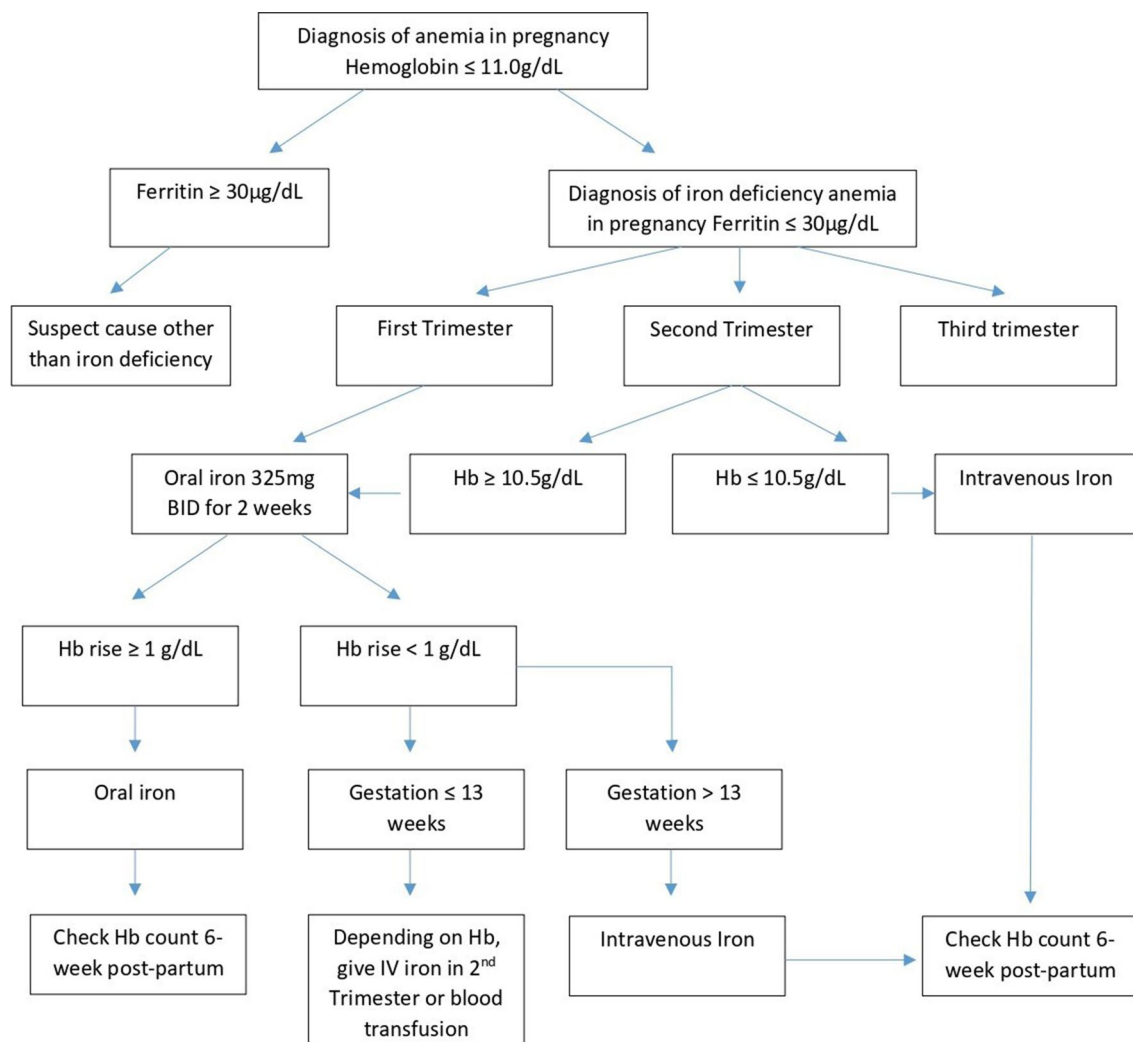
Iron deficiency anaemia, a condition characterised by insufficient iron levels in the body, is typically treated with oral iron supplements. Despite the fact that these supplements are generally safe and effective, certain adverse effects should be considered. Gastrointestinal discomfort is one of the most prevalent side effects of oral iron supplementation. It may cause nausea, vomiting, constipation, diarrhoea, and abdominal cramping. The severity of these symptoms can vary and may diminish as the body adjusts to the iron supplement. These adverse effects can be minimised by taking the supplement with food or by dividing the daily dosage into multiple doses [41].

Teeth discoloration is another adverse effect of oral iron. The teeth may turn black or grey after taking iron supplements. The side effect is more prevalent when the supplement is chewed as opposed to ingested whole. Staining can be avoided or minimised with the use of good oral hygiene techniques, such as brushing your teeth after taking the supplement. In certain instances, iron supplements taken orally can induce allergic reactions. Symptoms may include rash, itching, swelling, vertigo, and respiratory difficulties. It is critical to get medical help right once if any of these symptoms appear [42].

Additionally, iron supplements can inhibit the absorption of other medications. They can diminish the efficacy of certain antibiotics, thyroid medications, and osteoporosis treatment drugs. Although these adverse effects are possible with oral iron supplements, they are generally well-tolerated, and the majority of people do not experience serious issues. The comparison of oral and intravenous iron infusion has been shown in Table 2. However, if you are concerned about the side effects or encounter severe symptoms, it is essential that you seek the advice of your healthcare provider [41].

**Table 2** Comparison of oral vs intravenous iron infusion [43]

	Oral iron	Intravenous iron
Indications	Supplementation for patients at risk of IDA Nutritional IDA IDA due to menorrhagia IDA due to pregnancy	Functional IDA Poor iron mobilisation Gastrointestinal conditions (irritable bowel disease, celiac disease) Failure of oral iron treatment
Adverse effects	Primarily gastrointestinal (dose-dependent)	Primarily related to infusion reactions
Duration of therapy	Minimum of 3 months, often longer due to poor compliance	If the primary cause is addressed, only a single infusion or visit is necessary
Cost	Inexpensive but additional follow-up is necessary	Expensive due to drug infusion cost
Quality of life	Dependent on adverse effect Resolution of anaemia Multiple visits for lab testing	One time infusion No long-term compliance issue



**Fig. 3** Approach recommended for diagnosis and treatment of IDA in pregnancy (figure taken and modified from Raut) [49]

## Avoiding blood transfusion

Blood transfusions have long been effective in treating severe iron deficiency anaemia (IDA), especially when dietary iron therapy fails or swift correction is crucial. The reasons for avoiding transfusions during pregnancy remain unclear. A recent study comparing oral and intravenous (IV) iron treatments during pregnancy discovered that neither group required blood transfusions to manage anaemia, shedding light on alternative options for IDA control [44].

Two (0.9%) participants in the oral iron group required postpartum blood transfusions. Optimal therapeutic outcomes can be attained by administering larger, less frequent doses of iron in a safe and effective manner across different clinical scenarios. The primary goals of these

techniques are to achieve cost effectiveness, reduce the burden on health care system, and improve patient convenience.

## Association between *H. pylori* infection and IDA

The association between *H. pylori* infection and iron deficiency anaemia in pregnant women is a topic of increasing significance within the field of maternal and child health. *Helicobacter pylori*, an infectious bacterium that colonises the gastric mucosa, has the potential to cause chronic gastritis and hinder the absorption of essential nutrients, such as iron. This phenomenon assumes particular significance

during pregnancy, as the need for iron escalates to facilitate the development of the foetus and the expansion of maternal blood volume [45].

According to studies, *H. pylori*-infected pregnant women are more likely to experience iron deficiency anaemia. The infection's effect on the stomach's mucosal lining can impair iron absorption, worsening pregnancy's natural iron requirements. As a result, addressing *H. pylori* infection through appropriate medical interventions, such as antibiotics and proton pump inhibitors, is crucial to mitigate the risk of iron deficiency anaemia in expectant mothers. The prompt and appropriate identification and management of medical conditions during pregnancy can effectively enhance the well-being of both the expectant woman and the developing foetus, thereby mitigating the likelihood of adverse outcomes [46].

New evidence indicates that the Cag-A protein of *H. pylori* disrupts the transferrin/transferrin receptor iron absorption system. Rapid advances in iron absorption after eradication of *H. pylori* support a direct interaction between iron transport and iron absorption. Moreover, IDA is associated with *H. pylori*-induced carcinogenesis, highlighting the significance of *H. pylori* eradication in IDA patients; also, the infection is associated with an increased risk of IDA but not other micronutrient deficiencies in pregnancy [47, 48].

## Discussion

The “WHO” considers IDA as the most serious nutritional deficit that exists today, underlining how particularly vulnerable women are to it. This situation has the potential to have devastating repercussions on entire populations and serious consequences if neglected and addressed improperly. For specific clinical scenarios, intravenous iron therapy is a recommended, rapid, reliable treatment option. Supported by various controlled trials, it suggests a treatment approach for iron deficiency anaemia in pregnancy and postpartum (Fig. 3).

Intravenous iron administration is now widely used to prevent transfusions and quickly restore iron levels. The new formulations are seen as a breakthrough in treating iron deficiency anaemia and should be considered for treatment [50]. In developing countries, most of people are at risk of iron deficiency anaemia. It mainly affects the poorest and least educated people. *H. pylori*-infected pregnant women are more likely to experience iron deficiency anaemia, and strategic treatment to eradicate the infection should also be looked into. Therefore, such people will be benefitted the most from the elimination of IDA. Health practitioners will also be better able to determine the most efficient diagnostic and treatment measures, which are crucial in treating such a

serious health issue if they are aware of the extent and severity of the IDA problem both during pregnancy and in the non-pregnant female population. A comprehensive approach is crucial for addressing IDA's health and financial aspects. International experts in managing IDA among women and the general population have developed a consensus management guideline, highlighting the importance of a global strategy [51].

## Conclusions

It would be a good idea to think about a global, all-inclusive algorithm for managing IDA that offers several treatment options based on evidence and attends to regional issues. In contrast, resource shortages are a significant issue in developing countries where IDA is common. Because of this, it is important to make a programme that will work and make good use of the area resources. For such a programme to be successful and last, it may be important to make treating IDA a top priority and make more people aware of such a serious, long-lasting condition. The eradication of IDA will undeniably boost productivity and community health, yielding immense benefits in developing and wealthy nations alike, positively impacting both societies' well-being.

**Author contribution** All authors whose names appear on the submission (1) made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work; (2) drafted the work or revised it critically for important intellectual content; (3) approved the version to be published; and (4) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Availability of supporting data** Not applicable.

## Declarations

**Ethical approval and consent to participate** Not applicable.

**Consent for publication** Not applicable.

**Competing interests** The authors declare no competing interests.

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