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The Dire Need of a Suitable Algorithm for the Management of IDA in Pregnancy

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ABSTRACT

BACKGROUND/PURPOSE OF THE STUDY

Maternal anemia is associated with significant morbidity and mortality of both mother and offspring. The therapeutic options available for management of IDA during pregnancy include: oral administration of iron salts, blood transfusion and parenteral infusion of iron solutions. This review intends to suggest an algorithm that will aid medical professionals in identifying and treating iron deficiency during pregnancy.

METHODS: This algorithm was inspired by other streamlined simplified algorithms.

RESULTS: Dietary changes, oral iron supplements, intravenous iron, and blood transfusions are all part of the treatment for ID. There is growing evidence to support the use of parenteral iron preparations in frontline settings for pregnancy-related IDA in the second and third trimesters. A worldwide approach to the health and economic aspects of IDA should be taken into consideration, along with a consensus guideline developed by international specialists in managing IDA in women and the general population that includes intravenous iron therapy.

CONCLUSION: In treating maternal IDA, parenteral ISC is more efficient than LMWID and is linked to fewer adverse effects. Intravenous ferric carboxymaltose and intravenous iron sucrose were the most effective interventions for improving haemoglobin 4 weeks after starting treatment. Also, intravenous iron sucrose was found to be the most effective intervention for improving serum ferritin. It is worthwhile to take into account a global, all-encompassing IDA management algorithm that provides several evidence-based treatment alternatives and attends to regional issues.

KEYWORDS:IDA during pregnancy, intravenous iron sucrose, IDA management algorithm

I. INTRODUCTION

An exponential rise in iron demands during pregnancy can be attributed to expanding maternal blood volume and proliferation of the fetoplacental unit.[1]According to the WHO, anemia during pregnancy is defined as hemoglobin level of less than 11 g/dl.[2] Iron deficiency anemia can be defined as abnormal values on biochemical test results, increases in hemoglobin concentrations of more than 1 g/dL after iron treatment, or absent bone marrow iron stores as determined by a bone marrow iron smear. The latest update by ACOG classified trimester-wise anemia as hemoglobin (g/dL) and hematocrit (percentage) levels below: 11 g/dL and 33%, respectively, in the first trimester; 10.5 g/dL and 32%, respectively, in the second trimester; and 11 g/dL and 33%, respectively, in the third trimester.Analysis of serum ferritin levels can best diagnose iron deficiency in anemic patients.[3]

The global prevalence of anemic pregnant women was found to be 36.5%, according to data obtained in 2019. Africa, followed by South-East Asia, has the highest rate of anemia in pregnancy (57%) while South America had the lowest prevalence at 24.1%.[4]

Maternal anemia is associated with significant morbidity and mortality of both mother and offspring. Factors such as severe hemorrhage at delivery or postpartum and heart failure arising as a consequence of severe, untreated anemia leads to doubled risk of death in pregnant women with severe anemia as compared to those who without severe anemia. Negative fetal outcomes such as stillbirth, IUGR, low birth weight, premature birth and neonatal iron deficiency may develop as a consequence of maternal anemia.[5]

Previous studies have also established a deterioration in oxidative stress (OS) in iron-

deficient pregnant women. The physiological needs of pregnancy like increased oxygen requirement itself increases the OS of the body, which combined with IDA causes further worsening of OS. When the levels of reactive nitrogen and oxygen species (RNS and ROS) arising from OS exceed the maternal oxidant-antioxidant balance capacity, it may lead to complications like spontaneous preterm delivery and premature rupture of membranes. OS may negatively influence cellular signal pathways of the heart, resulting in growth, apoptosis, hypertrophy, inflammation, and remodeling of cardiac muscle. Studies have found a connection between OS triggered by hemodynamic alterations and cardiovascular diseases such as heart failure, cardiac arrhythmia, and arterial hypertension.[6]

The therapeutic options available for management of IDA during pregnancy include: oral administration of iron salts, blood transfusion and parenteral infusion of iron solutions. Supplementation with oral forms of divalent and trivalent iron salts for management of IDA is widely prevalent due to ease of preparation and distribution, low expense and no requirement of medical resources or supervision. Although, oral iron supplementation may exaggerate nausea, vomiting as well as hyperemesis gravidarum during pregnancy. Due to the presence of side effects, low systemic absorption and a slow and inconsistent response, it is not the most appropriate option in all cases.[1,7]

Blood transfusion although effective in severe cases of IDA requiring rapid correction of anemia, poses significant health hazards (RBC allo-immunization, volume overload and fetal hemolytic disease), is expensive and puts a strain on already scarce resources.The current AABB and the RCOG guidelines suggest a threshold of Hb <7 g/dl for transfusion and a threshold of <8 g/dl in patients with pre-existing cardiovascular disease. Cardiovascular status, availability of alternate treatment options and risk-benefit ratio should be considered before option for transfusion in iron-deficiency anemic pregnant women.[8]

Parenteral route of iron administration can be considered in patients showing insufficient response or intolerance to oral iron therapy, reduced gastric absorption and severe cases which necessitate rapid correction of anemia. IM iron following a test dose, is a cost-effective treatment for moderate anemia in pregnancy. Intravenous route has replaced IM iron therapydue to the associated adverse events like painful injection, dark discoloration of the skin, and the risk of myalgia, arthritis, hypersensitivity and lymphadenopathy.[8]

Various IV formulations to be administered intravenously include ferric carboxymaltose (FCM), iron sucrose (IS), and iron polymaltose (IP). Previously, intravenous administration of iron complexes were associated with fatal side effects and death but the recently developed formulations are safer and more effective.[7] A systematic review found significant increase in hemoglobin and ferritin associated with administration of IV iron therapy versus oral iron therapy for the management of IDA during pregnancy.[9]

II. DISCUSSION

Even in developed countries, pregnant women frequently develop overt IDA indicating insufficient iron consumption and inadequate physiologic adaptations to meet the increased demands of the body.[7]Despite the numerous treatment options available,IDA remains a crippling nutritional deficit in the world in the twenty-first century, highlighting that women are disproportionately at risk. Such a situation can have disastrous effects on entire populations and major repercussions if ignored and improperly treated. In light of this context, this review intends to suggest an algorithm that will aid medical professionals in identifying and treating iron deficiency during pregnancy. This algorithm was inspired by other streamlined simplified algorithms.

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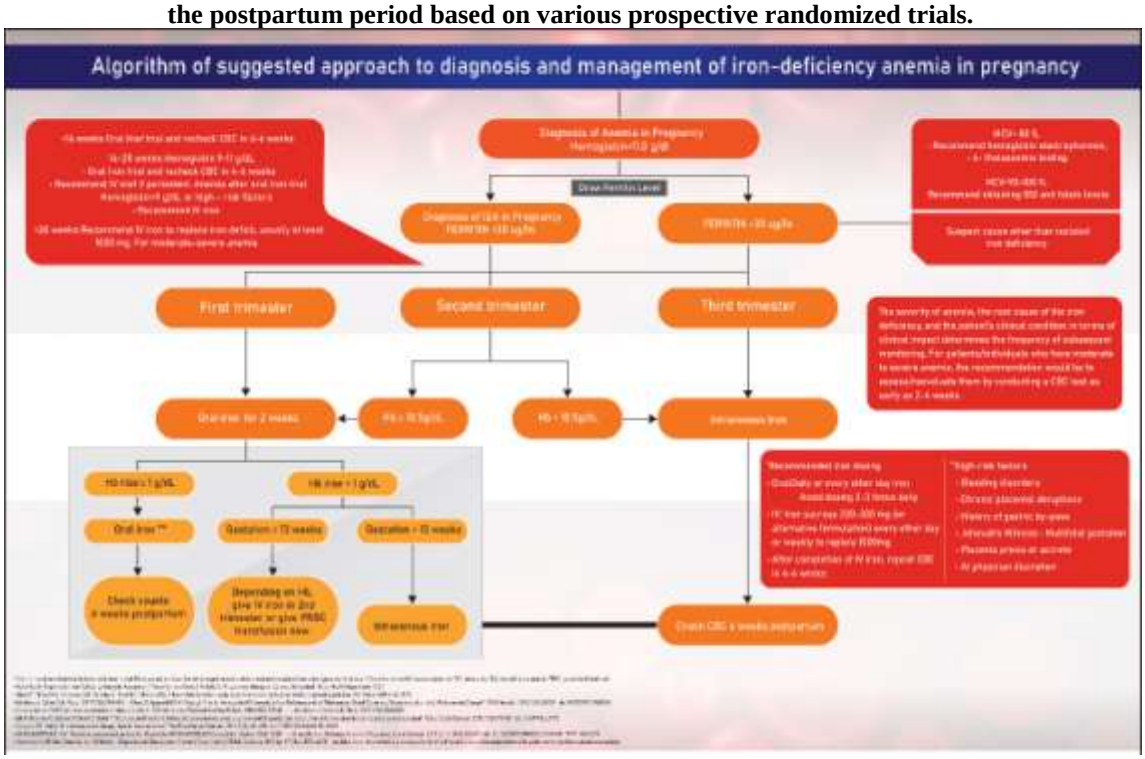
Figure 1 proposes an algorithm for the management of iron deficiency anemia throughout pregnancy and the postpartum period based on various prospective randomized trials.



Hemoglobin levels of less than 11 g/dL at any time during pregnancy are considered abnormal. The World Health Organization (WHO) defines anemia of pregnancy as hemoglobin (Hb) <11 g/dL, or hematocrit <33%, at any time during the pregnancy.[2] The CDC categorizes anemia during various stages of pregnancy as follows: first and third trimesters <110 g L^{-1}, second trimester <105 g L^{-1} and postpartum <120 g $L^{-}1$.[10]

Serum ferritin level is a standardized tool for measurement of total body iron stores which is universally available. Although a value <12–15 µg L^{-1} confirms the presence of iron deficiency, a value of <30 µg L^{-1} is extensively used for the same as it has higher sensitivity (92%) and similar specificity (98%).[10]

For screening of thalassemia, mean corpuscular volume (MCV) of less than 80 fL and/or mean corpuscular hemoglobin (MCH) value of less than 27 pg are considered the cut-off levels indicating a positive result. Recently established cut-off values of 74 pg for MCV and 28 fl for MCH were shown to possess higher sensitivity (94%) and are recommended.[11]

In people with the α-thalassaemia trait, the presence of other nutritional deficiencies such as iron, vitamin B12 and folic acid can affect MCH and MCV and make them unreliable in detecting thalassaemia carriers.[12]

Megaloblastic anemia (MA) usually develops due to a deficiency of vitamin B12 (cobalamin) or folate. A common clinical finding in MA is macrocytosis that can be detected months before the development of anemia. Macrocytosis of red blood cells (RBC) in adults is defined as a mean corpuscular volume (MCV) of greater than 100 fL. A complete blood count (CBC) is essential to confirm macrocytosis, the degree of anemia, and other features. Although increased MCV (>100 fL) is a classic feature, it may not always be present in patients with MA. Iron deficiency, thalassemia, chronic illnesses (causing active inflammatory states), or renal disease may normalize the MCV in patients with MA or even produce a microcytic picture.[13]

Clinical symptoms of anemia during pregnancy include fatigue, pallor, dizziness and weakness, palpitations, dyspnea, irritability and Pica. These symptoms are rather non-specific and cannot be relied on for an accurate diagnosis. It is recommended to draw blood for a complete blood count at the booking appointment as well as 28 weeks. On account of hemoglobin count being less than 11.0 g/dL, further testing for serum ferritin levels is required.Serum ferritin level of <30 µg L^{-1} indicates iron deficiency and warrants a trial of oral iron. On repeat testing at two weeks, a rise in hemoglobin of ≥1gm/dL, confirms the diagnosis of iron deficiency and supports continuation of oral

iron therapy. In pregnant women with a gestation of ≤ 13 weeks, who fail to elicit adequate response to oral iron therapy, an IV iron infusion can be initiated during the second trimester.[14]

IV iron therapy should be considered in pregnant women in the second trimester, who fail to respond or are intolerant to oral iron therapy. Also, it is recommended in women with confirmed diagnosis of iron deficiency and presenting a Hb <11 gm/dL after 34 weeks of gestation.[14,15]

An iron deficit of 1000 mg or more is commonly found in most pregnant women with moderate to severe iron-deficiency anemia. Total body iron deficit can be calculated using this formula (body weight in kg × [target hemoglobin level – actual hemoglobin level in g/dL] × 2.45) to determine the exact quantity of iron required.[16]

It is important to exclude hemoglobinopathy or folate and vitamin B12 deficiency before initiation of IV iron therapy in pregnant women. If levels of ferritin obtained are > 30 µg L^{-1}, evaluation of MCV levels can be used as a tool for further investigation. With MCV < 80 fL, hemoglobin electrophoresis and α-thalassemia testing is recommended to rule out any hemoglobinopathy. Assessment of folate or B12 deficiency is recommended if MCV is >90 -100 fL. Discrepancies in MCV levels are a reason to suspect causes of anemia other than isolated iron deficiency.[16]

According to recently concluded systematic reviews, when compared to oral iron therapy, IV iron therapy shows greater improvements in maternal Hb (WMD 6.6 g/L; 95% CI: 3.1–10.1 g/L) and ferritin (WMD 45.6 mg/L; 95% CI: 26.21–65.16 mg/L). Mild reactions elicited are fewer with IV iron administration compared to oral iron intake (RR 0.34; 95% CI: 0.20–0.57). Neonatal weight at birth is higher after maternal treatment with IV iron (WMD 58 g; 95% CI: 6–111 g).[15]

IV iron therapy is advantageous over oral therapy as it offers complete bioavailability with lesser GI side effects. Setting a slow infusion rate and providing symptomatic care, such as anti-emetics can help tackle commonly associated side effects like nausea, headaches, dizziness, hypertension, flushing and injection/infusion site reactions.[15]

A study proves that after 4 weeks of treatment, pregnant women receiving IV iron were 2.7 times more likely to achieve target hemoglobin levels than women taking oral iron.Similarly, higher hemoglobin levels after 4 weeks were reached by women in the IV iron group compared with women in the oral iron group. A lower rate of gastrointestinal adverse effects was observed in pregnant women provided with IV iron compared to those provided with oral iron.[17]

Recent IV iron formulations include iron polymaltose (IP), iron sucrose (IS) and ferric carboxymaltose (FC) are safer and more effective leading to better compliance. For IP, the maximum dose that can be administered at a time may be over 2500 mg. IV IP can significantly improve iron deficiency, however it poses a higher risk of side effects such as headache, symptomatic hypotension, back pain, heartburn, chest tightness, dyspnea, nausea, tachycardia, rash, and vomiting.[7]

FCis a macromolecular ferric hydroxide carbohydrate complex, with a high molecular stability, allowing for controlled delivery of iron to the cells. It is safe and effective IV iron to be administered during pregnancy and causes lesser side effects compared to oral iron. Furthermore, FCM does not cross the placenta. The maximum daily dose is 1000 mg/20 mL.[7]

A relatively newer medication, iron sucrose complex (IS) is presently the most often utilized iron preparation administered intravenously to treat IDA. IV IS complex is safe and efficacious in pregnancy and is associated with lesser side effects compared to oral iron therapy. Studies show an increase of the Hb concentration in 28 days from 1.3 to 2.5 g/dL compared with 0.6 to 1.3 g/dL in the groups treated with oral iron.[7] No test dose is necessary before initiation of IV IS therapy. The only drawback is that the maximum dose is limited to 300 mg in one sitting or 600 mg weekly. Anaphylaxis is uncommon, although infusion site erythema can be prevalent.[18]

Packed red blood cell (PRBC) transfusions are frequently used to treat inadequate iron levels during pregnancy. According to previous findings, antenatal usage of iron sucrose was linked to decreased incidence of PRBC transfusions during pregnancy in a small cohort. This therapy has a potential to reduce allogeneic blood transfusion rates, together with an earlier study linking intravenous iron sucrose with reduced PRBC transfusion.[19]

For patients with iron deficiency anemia who cannot tolerate, cannot absorb, or do not respond to oral iron, intravenous iron is preferred.[20]According to one study, individuals receiving ISC presented a larger mean increase in hemoglobin levels two weeks after therapy as compared to those receiving low-molecular-weight iron dextran (LMWID). Patients on LMWID reported more adverse events as compared to patients who received ISC (P = 0.024). In comparison to the ISC group, the estimated blood

loss after delivery was substantially larger in the LMWID group. Compliance was 100% and 75% in ISC group and LMWID group, respectively. In treating maternal IDA, parenteral ISC is more efficient than LMWID and is linked to fewer adverse effects.[21]

According to another systematic review, intravenous ferric carboxymaltose and intravenous iron sucrose were the most effective interventions for improving haemoglobin 4 weeks after starting treatment. Also, intravenous iron sucrose was found to be the most effective intervention for improving serum ferritin.[22]

Recombinant human erythropoietin (RhuEPO) in conjunction with IV iron, has been proved safe and effective for rapid correction of severe peripartum anemia, particularly in cases with antepartum and postpartum hemorrhage and patients with rare blood groups. However, due to lack of evidence, the routine use of EPO in pregnancy is not recommended except in cases with renal disease.[8]

III. CONCLUSION

The most common cause of anemia in pregnancy is still iron deficiency anemia (IDA). Untreated iron deficiency (ID) causes serious harm to the fetus and the mother. Overall, communities in the developing world are the most at risk, particularly the poorest and least educated groups who are disproportionately impacted by iron deficiency and thus stand to benefit the most from the eradication of IDA. Dietary changes, oral iron supplements, intravenous iron, and blood transfusions are all part of the treatment for ID. There is growing evidence to support the use of parenteral iron preparations in frontline settings for pregnancy-related IDA in the second and third trimesters.

PERSPECTIVE

A worldwide approach to the health and economic aspects of IDA should be taken into consideration, along with a consensus guideline developed by international specialists in managing IDA in women and the general population that includes intravenous iron therapy. It is worthwhile to take into account a global, all-encompassing IDA management algorithm that provides several evidence-based treatment alternatives and attends to regional issues. Without a doubt, the successful eradication of IDA will have a significant positive impact on productivity and community health, as well as result in significant health savings for both developing and developed countries.

REFERENCES

[1]. Martina S. Burn, Lisbet S. Lundsberg, Jennifer F. Culhane, Caitlin Partridge &Moeun Son. Intravenous iron for treatment of iron deficiency anemia during pregnancy and associated maternal outcomes, The Journal of Maternal-Fetal & Neonatal Medicine. 2023; 36:1.

[2]. World Health Organization. Global anemia reduction efforts among women of reproductive age: impact, achievement of targets and the way forward for optimizing efforts. World Health Organization. 2020.

[3]. Anemia in Pregnancy: ACOG Practice Bulletin Summary, Number 233. Obstetrics & Gynecology. 2021; 138(2): p 317-319.

[4]. Turawa E, Awotiwon O, Dhansay MA, Cois A, Labadarios D, Bradshaw D, Pillay-van Wyk V. Prevalence of Anemia, Iron Deficiency, and Iron Deficiency Anemia in Women of Reproductive Age and Children under 5 Years of Age in South Africa (1997-2021): A Systematic Review. Int J Environ Res Public Health. 2021; 18(23):12799.

[5]. Abd Rahman R, Idris IB, Isa ZM, Rahman RA, Mahdy ZA. The Prevalence and Risk Factors of Iron Deficiency Anemia among Pregnant Women in Malaysia: A Systematic Review. Front Nutr. 2022; 9:847693.

[6]. Veciha Özlem Bozkaya, Z. Aslı Oskovi-Kaplan, Ozcan Erel & Levent H. Keskin. Anemia in pregnancy: it's effect on oxidative stress and cardiac parameters, The Journal of Maternal-Fetal & Neonatal Medicine. 2021; 34:1, 105-111,

[7]. Garzon S, Cacciato PM, Certelli C, Salvaggio C, Magliarditi M, Rizzo G. Iron Deficiency Anemia in Pregnancy: Novel Approaches for an Old Problem. Oman Med J. 2020; 35(5):e166.

[8]. Tandon R, Jain A, Malhotra P. Management of Iron Deficiency Anemia in Pregnancy in India. Indian J Hematol Blood Transfus. 2018; 34(2):204-215.

[9]. Lewkowitz, A.K., Gupta, A., Simon, L. et al. Intravenous compared with oral iron for the treatment of iron-deficiency anemia in pregnancy: a systematic review and meta-analysis. J Perinatol. 2019; 39, 519–532.

[10]. Cappellini, MD, Musallam, KM, Taher, AT. Iron deficiency anemia revisited

(Review). J Intern Med. 2020; 287: 153–170.

[11]. Baliyan M, Kumar M, Nangia A, Parakh N. Can RBC Indices be used as Screening Test for Beta-Thalassemia in Indian Antenatal Women? J Obstet Gynaecol India. 2019; 69(6):495-500.

[12]. Idris, Faridah, et al. Optimal Mean Corpuscular Haemoglobin (MCH) Cut-Off Value for Differentiating Alpha Plus and Alpha Zero Thalassaemia in Thalassaemia Screening. Malaysian Journal of Medicine & Health Sciences. 2020; 16.

[13]. Torrez, M, Chabot-Richards, D, Babu, D, Lockhart, E, Foucar, K. How I investigate acquired megaloblastic anemia. Int J Lab Hematol. 2022; 44: 236– 247.

[14]. Pavord, S., Daru, J., Prasannan, N., Robinson, S., Stanworth, S., Girling, J. UK guidelines on the management of iron deficiency in pregnancy. Br J Haematol. 2020; 188: 819-830.

[15]. Benson CS, Shah A, Frise MC, Frise CJ. Iron deficiency anaemia in pregnancy: A contemporary review. Obstet Med. 2021; 14(2):67-76.

[16]. Govindappagari et al., Contemporary OB/GYN Journal. 2021; 66(7).

[17]. Govindappagari S, Burwick RM. Treatment of iron deficiency anemia in pregnancy with intravenous versus oral iron: systematic review and meta-analysis. Am J Perinatol. 2019; 36(4):366-376.

[18]. Jose, A., Mahey, R., Sharma, J.B. et al. Comparison of ferric Carboxymaltose and iron sucrose complex for treatment of iron deficiency anemia in pregnancy-randomised controlled trial. BMC Pregnancy Childbirth. 2019; 19, 54.

[19]. Valdes, Eduardo Ernesto MD; Gallo, Danielle; Payero, Elfy; Rezai, Shadi; Henderson, Cassandra MD. The Efficacy of Intravenous Iron Sucrose in Treating Iron Deficiency Anemia of Pregnancy [23D]. Obstetrics & Gynecology. 2019; 133 - p 49S-47S.

[20]. James AH. Iron Deficiency Anemia in Pregnancy. Obstet Gynecol. 2021; 138(4):663-674.

[21]. Samsudin S, Dulasi M, Sany S, Balanathan K, Chong SE, Ali A. Safety and Efficacy of Intravenous Iron Sucrose versus Low Molecular Weight Iron Dextran for Treatment of Iron Deficiency Anemia in Pregnancy: A Randomized Controlled Trial. Int J Womens Health. 2020; 12:1259-1270.

[22]. Rogozińska, Ewelina et al. "Iron preparations for women of reproductive age with iron deficiency anaemia in pregnancy (FRIDA): a systematic review and network meta-analysis." The Lancet. Haematology.2021; 8(7): e503-e512.

[23]. Government of British Columbia. Iron Deficiency – Diagnosis and Management [Internet]. Government of British Columbia. 2019 Apr 17 [cited 2023 Jul 21]. Available from: https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/iron-deficiency#oral-iron-response