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Research progress on iron deficiency anemia during pregnancy

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Abstract: *Within the female life cycle, anemia constitutes a highly prevalent disease category, with the primary etiological factors encompassing malnutrition, deficiencies in iron, folic acid, vitamin B12, and other micronutrients, schistosomiasis infection, acquired immunodeficiency syndrome (AIDS), as well as hereditary hemoglobin abnormalities such as thalassemia. The clinical impact of anemia varies according to the severity and duration of the condition. In addition to the unique physiological changes during pregnancy, anemia may also precipitate adverse gestational outcomes, including low birth weight and preterm delivery, with the degree and persistence of anemia playing a decisive role. Furthermore, severe non-gestational anemia can likewise engender a multitude of deleterious consequences, including low birth weight and premature birth. This paper aims to provide a comprehensive diagnostic assessment framework for iron deficiency and iron deficiency anemia during pregnancy, delving into the potential detrimental impacts of such conditions on maternal and offspring health, and proposing targeted therapeutic interventions and preventive measures accordingly.*

Keywords: *iron deficiency during pregnancy, anemia, heavy menstrual bleeding*

1. Introduction

Iron deficiency anemia (IDA) is a ubiquitous global public health challenge, impacting both developed and developing nations, and posing a significant threat to individual health status and quality of life. Among the reproductive-age female population, excessive menstrual bleeding and adverse gestational conditions constitute key risk factors precipitating IDA. [1-2]Regrettably, the majority of reproductive-age women afflicted with IDA currently lack adequate clinical assessment and appropriate treatment, a state of affairs that not only jeopardizes maternal health, but also exerts detrimental long-term consequences on offspring.[3]

2. Iron Balance in the Human Body

The diagnostic criteria for gestational anemia recommended by the Centers for Disease Control and Prevention (CDC) in the United States define anemia as hemoglobin (Hb) or hematocrit (Hct) values below the 5th percentile of the corresponding reference range for the healthy population. [4]Specifically, Hb <11 g/dL and Hct <33% in early pregnancy, as well as Hb <10.5 g/dL and Hct <32% in mid-pregnancy, are considered anemic. Given the potential adverse impact of iron deficiency anemia (IDA) on maternal and fetal health, early diagnosis is of utmost importance.[5]Given the multifactorial etiology of anemia, the diagnosis should not rely solely on Hb values. To establish a definitive diagnosis, a comprehensive assessment of red blood cell indices and serum ferritin (SF) levels is necessary. SF is one of the most reliable indicators of iron deficiency, and it is recommended to perform SF screening in early pregnancy. An SF <30 μg/L may suggest depletion of iron stores, and even in the absence of overt anemia, the diagnosis of IDA should be considered, and timely iron supplementation initiated.[6]However, in the presence of inflammation or chronic disease, ferritin levels may be normal or elevated due to its characteristics as an acute-phase protein, in which case the evaluation should be accompanied by C-reactive protein (CRP) assessment to exclude the interference of infection or inflammation. If CRP is elevated, it is advisable to re-evaluate the SF level after the inflammation is controlled.[7]

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3. Causes of IDA

For patients without anemic symptoms, routine SF monitoring during pregnancy is not necessary, and Hb concentration should be assessed periodically (every three months). When the SF level approaches the critical value (around 30 μg/L), in addition to CRP testing, other diagnostic investigations, such as transferrin saturation and serum iron determination, should be performed.[8]

If the SF is normal, but the transferrin saturation is <15%, it may indicate latent iron deficiency, as transferrin releases more iron to meet the increased demand for erythropoiesis. Given that serum iron is influenced by various factors, the assessment of transferrin levels can enhance the diagnostic accuracy. In the setting of normal SF and elevated CRP, soluble transferrin receptor (sTfR) can serve as an additional diagnostic marker, as its increase reflects iron deficiency or increased cellular iron demand. The elevated sTfR levels during pregnancy are associated with enhanced erythropoietic stimulation and iron-dependent cell proliferation.[9]

Some studies have suggested that lower sTfR concentrations in early pregnancy may be related to suppressed erythropoiesis, and sTfR levels are not affected by infection or inflammatory response, providing additional reference for the diagnosis of gestational IDA.[10]

The impact of iron deficiency anemia (IDA) on erythropoiesis often occurs against the backdrop of the physiological anemia of pregnancy, a phenomenon that is widely observed in mammals. [11]It is hypothesized that this physiological anemia serves to optimize placental perfusion by reducing maternal blood viscosity and to facilitate the supply of oxygen and nutrients to the fetus through the expansion of the red blood cell (RBC) mass. [12]Starting from approximately the 6th week of gestation, the growth of plasma volume outpaces that of the RBC mass, reaching a peak around 24 weeks of pregnancy, with the plasma volume increasing by 40%-50% compared to early pregnancy.[13]

4. Diagnosis of IDA

Since the parameters used clinically to diagnose anemia, including hematocrit (Hct), hemoglobin (Hb) concentration, and circulating RBC count, are all expressed based on the concentration in the total blood volume, the expansion of plasma volume leads to a decrease in these parameters, manifesting as an "anemic" state. Although Hb concentration, Hct, and RBC count are to some extent used as diagnostic criteria for anemia, they actually reflect a reduction in the RBC mass per unit of body weight. [14]Based on this standard, the physiological anemia of pregnancy is not a true anemic state: the RBC mass actually increases by 15%-25% during pregnancy, but this increase is masked by the dilutional effect of the expanded plasma volume.[15]This process is driven by the rise in serum erythropoietin (EPO) concentrations during the second and third trimesters of pregnancy,[16]and is facilitated or potentially constrained by the availability of iron. Pregnant women who receive iron supplementation exhibit more pronounced RBC mass expansion, while those with inadequate iron stores in early pregnancy have limited RBC mass growth. However, when iron supply is sufficient, the upper limit of RBC mass expansion is determined by the regulation of EPO, rather than by increasing the availability of iron.[17]

5. Physiological anemia during pregnancy

Given the dynamic balance between plasma volume and RBC mass, in addition to the physiological anemia of pregnancy, the potential causes of Hb concentrations <11 g/dL in early pregnancy and <10 g/dL in mid-to-late pregnancy should be further explored.[18] In the final stages of pregnancy, maternal plasma volume typically decreases, leading to an increase in Hct, Hb, and circulating RBC count. Maternal blood volume usually returns to pre-pregnancy levels within 1 to 6 weeks after delivery, while maternal erythropoiesis increases in late pregnancy and normalizes around one month postpartum.[19]

6. Treatment of IDA

The treatment strategy for iron deficiency anemia (IDA) must be formulated based on the underlying etiology and the severity of the condition. When determining the treatment plan, several key factors must be carefully weighed, including the remaining time before delivery, the severity of the anemia, the presence of other risk factors, the potential maternal complications, and the patient's personal preferences.

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The administration of iron supplements can be achieved through oral or non-enteral routes. Starting from the mid-trimester of pregnancy, non-enteral iron therapy is considered a more suitable option. Among the non-enteral routes, intravenous (IV) administration is regarded as the most appropriate method, whereas intramuscular (IM) iron injections are generally not recommended due to their slower absorption rate and the increased risk of adverse events, such as pain and aseptic abscesses.[20]

6.1.Oral iron

Oral iron supplementation is the primary treatment modality for mild iron deficiency (ID) during pregnancy. Various oral iron formulations are available, including ferrous (II) salts, iron (III) polymaltose complexes, and liposomal iron preparations.

6.2. Iron (II) salts

For the treatment of iron deficiency anemia, three ferrous salt formulations are available for selection, namely ferrous sulfate, ferrous gluconate, and ferrous fumarate. These preparations have not demonstrated significant therapeutic superiority, and their incidence of adverse effects is comparable. For women afflicted with iron deficiency anemia, the recommended daily elemental iron supplementation is 100-200 milligrams, and studies indicate that doses below 100 milligrams per day may be insufficient to meet the treatment requirements.

The absorption efficiency of ferrous salts is relatively low and exhibits substantial individual variability, with their absorption process potentially being impaired by mucosal damage and the intake of specific foods. Therefore, it is recommended to administer these supplements on an empty stomach, one hour before meals, accompanied by a glass of orange juice or another beverage rich in vitamin C, to enhance the absorption efficacy.

Regarding the frequency of iron supplementation, there is currently a lack of conclusive evidence demonstrating the equivalence of weekly or intermittent oral iron administration compared to daily continuous use. During the treatment course, follow-up assessments should be scheduled at 2-4 weeks to evaluate the effectiveness of the therapy. Once the hemoglobin level has been restored to normal, it is advised to continue oral iron supplementation for at least 4-6 months, until the serum ferritin concentration reaches approximately 50 ng/mL, and the transferrin saturation is maintained at a minimum of 30%.

6.3. Iron (III) Polygalactose Complex

Iron(III) polymaltose complex (IPC) is a form of oral iron supplement classified as a sustained-release formulation. Its distinctive feature lies in the fact that the polymaltose serves as a membrane encapsulating the trivalent iron, effectively attenuating the release rate of the elemental iron from the complex, thereby mitigating the occurrence of adverse effects. Furthermore, when co-administered with food, the bioavailability of IPC is enhanced.

The recommended dosage for clinical use is 100-200 milligrams per day. Compared to traditional ferrous salt preparations, IPC has demonstrated comparable therapeutic efficacy, but with superior safety profiles, a conclusion that has been validated by multiple studies. Although research on the use of iron polymaltose (IP) during pregnancy is relatively limited, there have been no reports of serious adverse events to date.

6.4. Liposomal iron

Liposomal iron is an innovative oral iron supplement, composed of ferric pyrophosphate complexed with ascorbic acid, and delivered via a phospholipid membrane. The distinctive feature of this formulation is the avoidance of direct contact with the intestinal mucosa, thereby achieving enhanced bioavailability and a reduced incidence of adverse effects.

Although liposomal iron holds promising prospects for application during pregnancy, the currently available clinical data remains relatively limited. Nonetheless, this novel iron preparation has demonstrated the potential to address the challenges associated with conventional oral iron supplements, particularly in terms of improving tolerability and therapeutic efficacy.

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6.5. Intravenous injection of iron

In specific clinical scenarios, such as suboptimal or non-responsive oral iron therapy, malabsorption disorders, intolerance to oral iron supplements, poor patient compliance, or the need for rapid and comprehensive treatment (e.g., placenta previa-related bleeding, late pregnancy), the transition from oral to intravenous iron therapy may be considered.

Historically, intravenous iron preparations have been limited in their clinical application due to the potential for adverse events, including severe hypersensitivity reactions, shock, and even fatality. However, the development of novel iron complexes in recent years has significantly enhanced their efficacy, safety, and patient acceptability.

Specifically, the use of iron sucrose during pregnancy has been strictly limited due to its high incidence of adverse reactions and potential for severity. While iron gluconate has not been associated with severe adverse events, its practical utility is constrained by the need for multiple infusions, high medical costs, and suboptimal patient compliance. Furthermore, the molecular stability of iron gluconate is relatively low, rendering it unsuitable for use in late pregnancy.

Intravenous iron therapy, by bypassing the intestinal iron absorption and protein-binding processes, has emerged as an effective alternative to oral iron supplements. The latest intravenous iron products, through tighter binding of iron to carbohydrate cores, have effectively reduced the release of free iron, thereby mitigating the risk of oxidative cell and tissue damage. Free iron can induce the generation of reactive oxygen species (such as hydroxyl radicals and superoxide), but the new formulations, by limiting free iron, have successfully avoided the associated severe consequences.The most recent intravenous iron products support single-dose, high-dose administration, further enhancing the convenience and efficiency of this therapeutic approach.

6.6. Sucrose iron

Intravenous iron sucrose (IS) complexes have demonstrated superior safety profiles compared to oral iron supplements, and have been validated as a secure and efficacious therapeutic modality during pregnancy. Research data indicates that in patients receiving intravenous IS complexes, hemoglobin concentrations increased significantly from 1.3 g/dL to 2.5 g/dL within 28 days, whereas the range of improvement in the oral iron therapy group was between 0.6 to 1.3 g/dL.

To ensure safety, the maximum single-dose administration should be limited to 200 mg or less. Additionally, the infusion duration must be appropriately managed, with a minimum of 15 minutes for a 100 mg dose and at least 30 minutes for a 200 mg dose.

These measures serve to mitigate potential adverse events and optimize the therapeutic efficacy of intravenous IS complexes, which have emerged as a secure and effective alternative to oral iron supplementation, particularly during the gestational period.

6.7. Iron based Galactose

Intravenous iron sucrose (IS) complexes have demonstrated remarkable clinical efficacy in improving hematological parameters. However, it is noteworthy that this therapeutic modality has been associated with an increased incidence of adverse events, including headache, symptomatic hypotension, back pain, heartburn, chest discomfort, dyspnea, nausea, tachycardia, skin rashes, and vomiting.

With regards to iron polymaltose (IP), the maximum single-dose administration may reach or exceed 2500 mg, and the duration required to complete the infusion of the full dose can range from 4 to 5 hours.

These factors underscore the need for careful patient monitoring and dose titration when utilizing intravenous iron therapies, in order to balance the substantial benefits in hematological optimization with the potential risks of adverse reactions. Meticulous clinical management is essential to ensure the safe and effective implementation of these advanced iron supplementation strategies.

6.8. Intravenous iron supplements

Intravenous iron carboxymaltose complexes (such as Ferinject®) are considered the preferred

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intravenous iron therapy for the management of iron deficiency during pregnancy. These complexes exhibit exceptional molecular stability, ensuring their robust presence within the body. Multiple randomized controlled trials have consistently demonstrated that Ferinject, as an intravenous iron supplement during pregnancy, is not only safe and effective, but also associated with a lower incidence of adverse events compared to oral iron preparations. Crucially, these complexes do not cross the placental barrier, thereby safeguarding the well-being of the fetus.

Regarding dosing, the maximum recommended daily dose of Ferinject is 1000 mg/20 mL, with an infusion rate to be maintained within the range of 100-500 mg/min. For doses ranging from 500-1000 mg, to ensure safe and effective administration, the infusion should be carried out over a duration of at least 15 minutes.

These factors underscore the clinical advantages and the robust safety profile of intravenous iron carboxymaltose complexes, such as Ferinject, in the management of iron deficiency during the critical gestational period, while prioritizing both maternal and fetal well-being.

7. The impact of IDA on the mother fetus relationship

Despite the World Health Organization (WHO) designating the prevention and treatment of iron deficiency anemia as a key priority, the issue remains a pressing concern in numerous developing countries. The impact of anemia varies depending on the severity, duration, and stage of pregnancy. The WHO classifies anemia into three categories based on hemoglobin levels: mild (10–10.9 g/dL), moderate (7–7.9 g/dL), and severe (<7 g/dL). [21]The association between mild anemia and adverse maternal-fetal outcomes remains controversial, with some studies suggesting that chronic mild anemia may not significantly impact the normal course of pregnancy and delivery.[22] However, emerging evidence increasingly indicates that iron deficiency may affect infant myelination, potentially leading to long-term impairments in cognitive function and learning abilities in children. Proactive intervention for mild anemia is crucial to prevent its progression to moderate or severe forms, as moderate and severe anemia are closely linked to increased maternal-fetal mortality and morbidity, requiring higher-dose iron therapy.[23]

Given the above, every case of anemia during pregnancy should be treated to prevent adverse perinatal outcomes and maintain optimal hemoglobin levels (10-12 g/dL) during gestation, with a threshold of <11 g/dL to achieve better overall outcomes.

The strong association between iron deficiency anemia and low birth weight, as well as preterm birth, has been extensively documented. [24]Anemia during mid-pregnancy significantly increases the risk of preterm delivery, which may be attributed to the chronic hypoxic state induced by anemia, triggering a stress response and increasing the secretion of corticotropin-releasing hormone (CRH), a well-established risk factor for preterm birth. Additionally, oxidative damage to red blood cells and the feto-placental unit may further exacerbate the risk of preterm delivery.

Beyond the early gestational period, maternal anemia significantly elevates the risk of preterm birth, with the association being most pronounced during late pregnancy, a finding consistently reported across multiple studies. Preterm infants not only face the risk of growth restriction but also the threat of impaired psychomotor development. A negative correlation between mid-pregnancy hemoglobin levels and birth weight has been reported, while hemoglobin levels in late pregnancy are a key determinant of birth weight, as this is the stage of rapid fetal growth with peak demands for iron and other micronutrients. This explains the significant association between late-pregnancy hemoglobin levels and low birth weight. One study found that infants born to anemic mothers at delivery had a 5.7-fold higher risk of anemia compared to those born to non-anemic mothers.[25]

8. Discussion

Despite iron deficiency anemia during pregnancy being a common syndrome with effective diagnostic and treatment modalities, there remains ample scope for further research to deepen the understanding of its pathogenesis and optimize its management. This review article explores several key research directions in this domain.[26]

A crucial area of focus is the exploration of the most efficient screening strategies. Currently, professional guidelines tend to favor anemia screening as the initial step in identifying iron deficiency anemia, with precise assessment of iron status often limited to high-risk patient populations. This raises

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an important question: should the introduction of specific iron status testing be considered to replace or complement universal anemia screening? If this approach is not feasible, then what hemoglobin/hematocrit threshold would most effectively identify iron deficiency anemia?It is hoped that future research will address these existing challenges and propose practical solutions. Advancing the understanding of the underlying pathogenic mechanisms and optimizing the management of iron deficiency anemia during pregnancy remain vital areas of investigation, with the potential to significantly improve maternal and fetal health outcomes.

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