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" *Umbilical Cord Hepcidin as a Predictive Biomarker for Neonatal Iron Deficiency* "

Authors

- Dalia Adel Sabet [1] , Rasha Emad Bader [2] , Nesrin Mossad Handoka [3] ,
- Mona Mahmoud Ismail [4]

[1] M. B. B. Ch, Pediatric Resident at University Hospitals of Faculty of Medicine, Port Said University

[2] MD in Clinical Pathology, Professor of Clinical Pathology Department, Faculty of Medicine, Port-Said University

[3] MD in Pediatric Medicine, Professor of Pediatrics and Neonatology Department, Faculty of Medicine, Port Said University

[4] MD in Pediatric Medicine, Lecturer of Pediatrics at Pediatrics and Neonatology Department, Faculty of Medicine, Port Said University

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https://muj.journals.ekb.egdean@med.psu.edu.eg

vice_dean_postgraduate@med.psu.edu.eg

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ABSTRACT:

For many physiological processes, iron is a vital micronutrient., particularly in fetal growth and neurodevelopment. In the course of pregnancy, maternal iron needs increase significantly to assist expanding red cell mass, placental function, and fetal demands. Impairment in iron homeostasis may result in fetal and iron deficit in newborns,a condition linked to adverse cognitive, motor, and behavioral outcomes in later life. Hepcidin, a peptide hormone produced by the liver, functions as the principal overseer of systemic iron metabolism. This mechanism governs the absorption and release of iron via the interaction with the iron exporter ferroportin, leading to its internalization and eventual degradation.

In recent years, umbilical cord hepcidin has garnered attention as a potential biomarker for assessing iron status in neonates. This review synthesizes current evidence on iron metabolism during pregnancy, The intricate mechanisms underlying fetal iron deficiency and the pivotal function of hepcidin in modulating the transfer of iron between mother and fetus. Furthermore, it explores the utility of measuring umbilical cord hepcidin levels to identify neonates at risk for iron deficiency anemia and discusses the clinical implications and challenges related to assay variability, interpretation, and implementation in different populations. Understanding the regulatory mechanisms of hepcidin in fetal and neonatal contexts may lead to improved screening strategies, targeted supplementation, and ultimately better neurodevelopmental outcomes.

Keywords: Hepcidin, Ferritin, Neonatal Anemia, Iron Deficiency

INTRODUCTION

Protecting brain growth is an important public health goal around the world because it sets the stage for a healthy and useful life. **(black et al., 2017).**

In prenatal period and infancy, iron deficiency (ID) can result in irreparable brain damage. Since newborns in the US are not usually checked for iron status, it is uncertain how common neonatal ID is **(Campbell et al, 2022).**

Fetal morbidity and mortality are significantly increased by anemia, particularly in developing countries. Almost all infants exhibit anemia characterized by a hemoglobin (Hb) concentration of no less than 10 g/dL at term; in the majority of instances, this phenomenon is a physiological occurrence rather than indicative of a deficiency or an underlying hematologic disorder.**(Means, 2020).**

Haemoglobin (Hb) is a protein that helps red blood cells (RBCs) carry out their main job of carrying oxygen. Maternal plasma volume rises by 50% throughout pregnancy, reaching its peak between weeks 28 and 36. RBCs, on the other hand, grow by 15% to 25% in order to boost their ability to deliver oxygen and to eliminate waste through the placenta **(Elmore & Ellis, 2022).**

Ferroportin and hepcidin are two hormones that are crucial for the distribution and control of iron **(Ganz, 2019).**

Anemia

The defining characteristic of anemia is a deficient quantity of healthy red blood cells within the body. Oxygen is supplied to body tissues by red blood cells. **(Elghetany & Banki, 2022).**

Anaemia can be defined in two ways: quantitatively, as a decrease in the number of circulating erythrocytes, or functionally, as a condition where the amount of oxygen-carrying erythrocytes is insufficient to meet metabolic demands. Hemoglobin (Hb), hematocrit, and red blood cell count values that fall below the established age- and sex-adjusted norms serve as indicators for the identification of anemia in clinical practice.. It's crucial to define anemia using the proper ranges. **(Zierk et al., 2019).**

The association of anemia with heightened mortality and morbidity is evident, encompassing neurological complications, an elevated risk of low birth weight, susceptibility to infections, and the potential for heart failure. When dealing with a kid who has anemia, thorough medical history—especially on food, exposures to the environment, and family history—often provides crucial hints for the diagnosis. by Physical examination the dysmorphic characteristics might point to syndromic causes of anemia such as thalassemic features **(Gallagher, 2022).**

Classification of anemia, morphological (based on the MCV) and pathophysiological (based on the medullary regenerative capacity, determined by the

reticulocyte response) classifications of anemia are complementary and required for the etiological diagnosis approach **(Rosich del Cacho & Mozo del Castillo, 2021).**

This review does not provide an exhaustive examination of the diverse classifications of anemia. Iron deficiency anemia represents the most prevalent form ; however, clinicians must recognize the potential coexistence of various forms of anemia and conduct appropriate screenings. In the third trimester, there is a notable peak in plasma levels, resulting in the hemodilution of iron indices. It is essential to differentiate between the standard physiological hemodilution that occurs during pregnancy, acute blood loss, chronic conditions, and iron deficiency anemia **(Elmore & Ellis, 2022).**

Iron Deficiency Anemia

The prevalence of iron deficiency and iron deficiency anemia is a significant concern worldwide **(Camaschella, 2015).** In developing nations, iron deficiency stands out as the most prevalent nutritional inadequacy impacting children. Conversely, in developed nations, although the incidence is on the decline—partly due to the iron fortification of infant formulas and cereals—it continues to be a significant contributor to the prevalence of anemia in children and adolescents.

The relationship between iron deficiency, irrespective of the presence of anemia, is particularly significant due to its association with cognitive impairments, some of which may be reversible **(McCann et al., 2020).**

Throughout gestation, there exists an increased requirement for iron, attributable to the augmentation of red blood cell synthesis and the expansion of the overall blood volume in circulation. Iron is essential for the effective transport of oxygen to the developing fetus. The fetus accumulates iron throughout pregnancy, a vital component for its initial months of life. Consequently, pregnant women are prone to the onset of iron deficiency anemia

(Ceulemans et al., 2023).

The assessment of iron status is seldom performed during the initial phases of infancy, given that national surveillance through the National Health and Nutrition Examination Survey (NHANES) generally commences in the toddler years. Research suggests that the presence of intellectual disability during early infancy serves as a considerable risk factor for the continuation of such disabilities in later infancy, as well as for hindered cognitive development. The accumulation of iron stores during gestation plays a vital role in supporting cognitive development in infants and young children, as cognitive impairments can only be partially addressed through iron supplementation after birth **(Campbell et al., 2022).**

Iron metabolism

Physiology of Serum Iron Distribution

The metabolism of iron in humans involves the intricate chemical reactions that govern iron homeostasis across both systemic and cellular dimensions. Iron is a crucial element for the body, though it may also present potential toxicity risks **(Ems et al., 2023).**

Iron plays a crucial role in numerous metabolic processes in the human body, such as DNA synthesis, electron transport, and oxygen transport. In contrast to other minerals, the regulation of iron concentrations within the human body is solely governed by the mechanism of absorption **(Ems et al., 2023).**

The process of iron excretion operates without regulation, manifesting through various means such as loss via perspiration, menstruation, the process of hair and skin cell shedding, alongside the rapid turnover and removal of enterocytes, is noteworthy. Within the human organism, iron predominantly resides in erythrocytes as part of the heme compound known as hemoglobin, with an approximate quantity of 2 g found in males and 1.5 g in females. Furthermore, it is found in smaller quantities within storage compounds such as ferritin and hemosiderin, and is also present in muscle cells in the form of myoglobin. Iron is present in hemoproteins and non-heme enzymes that participate in oxidation-reduction reactions and electron transfer, such as cytochromes and catalase **(Ems et al., 2023).**

Furthermore, around 2.2% of the overall body iron is found within the labile pool, a poorly characterized and reactive iron reservoir that generates reactive oxygen species through the Fenton Reaction, engaging with a class of medications referred to as chelators. Iron chelators play an essential role in addressing iron overload, a condition frequently encountered in patients undergoing transfusion therapies for thalassemias and various forms of anemia **(DeLoughery, 2019).**

Ferroportin and hepcidin are two critical hormones that significantly influence the distribution and regulation of iron in the body. Ferroportin functions as an essential protein facilitating the movement of iron from duodenal enterocytes, recycled red blood cells, and iron-storing hepatocytes into the circulatory system. Hepcidin, synthesized by liver hepatocytes, interacts with ferroportin in conditions of elevated serum iron levels, thereby reducing the bioavailability of iron. The liver modulates serum iron concentrations by elevating hepcidin synthesis in response to iron surplus and diminishing hepcidin levels during instances of iron scarcity **(Fisher & Nemeth, 2017).**

While iron is essential for the maintenance of life, an excess can be harmful. The existence of unregulated free iron can promote the generation of detrimental reactive oxygen species (ROS) and free radicals, primarily through Fenton chemistry. The Fenton reaction involves the interaction of iron(II) ions with hydrogen peroxide,

resulting in the formation of the highly reactive hydroxyl radical (•OH). The reaction can be expressed as follows: $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + \bullet OH$ **(Shadid, 2018).**

Ferritin represents the cellular adaptation to these challenges. Ferritin functions as the ubiquitous iron storage protein found in both prokaryotic and eukaryotic life forms throughout the natural world. Ferritin is defined by its hollow cage structure, wherein iron is sequestered as an iron(III) mineral within the protein shell, capable of accommodating around 4500 iron ions in an 8 nm cavity**(Shadid,2018).**

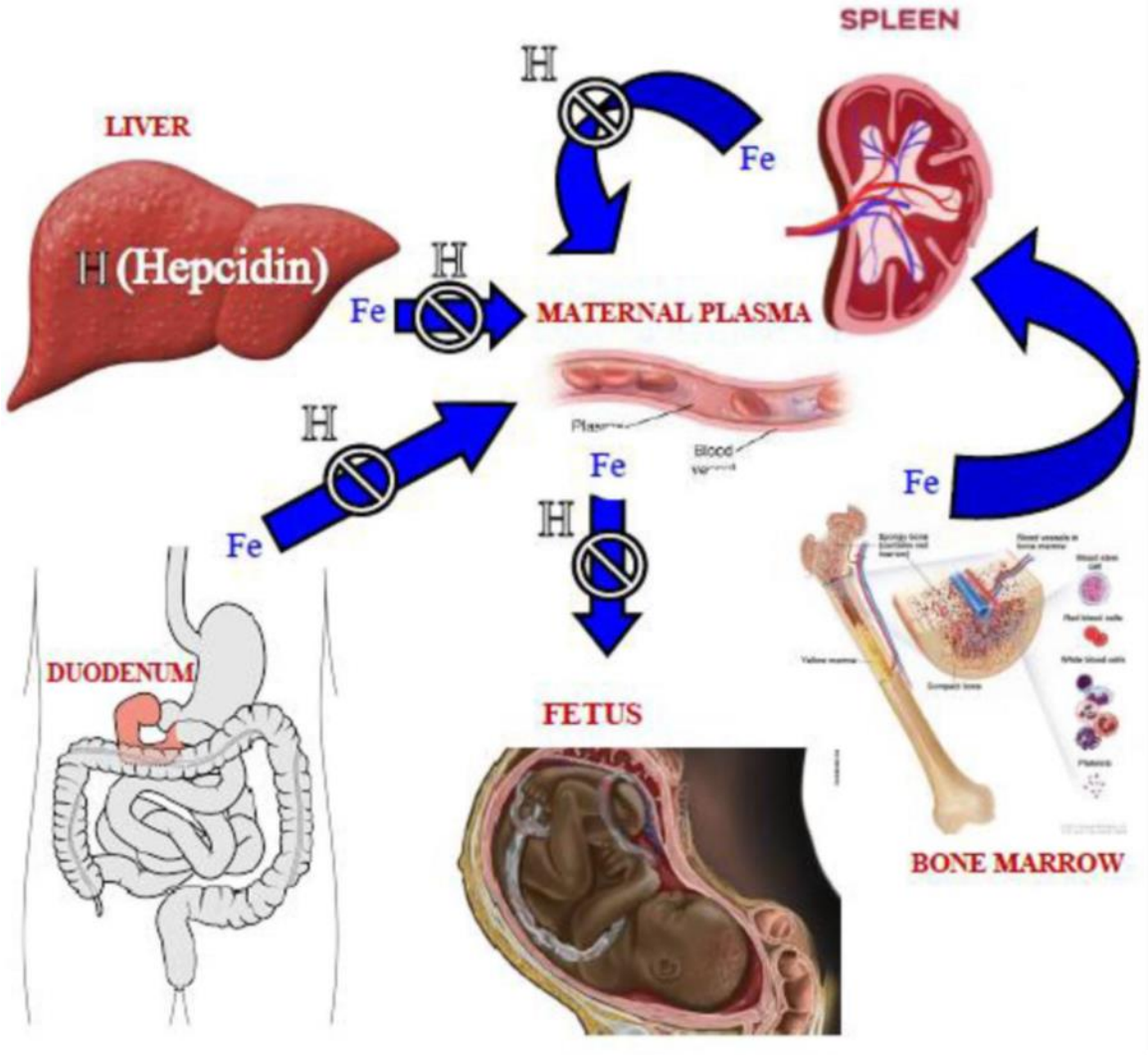

Figure 1 ; Hepcidin Production **(Fisher & Nemeth, 2017).**

The liver's production of hepcidin functions to obstruct the movement of ferroportin from the liver, duodenum, and spleen into maternal plasma, in addition to its transport to the fetus through the placenta (blue arrows indicate the routes of ferroportin transfer).

Abbreviations: H, Hepcidin; Fe, ferroportin.

The regulation of serum iron availability is essential for sustaining equilibrium., achieved through mechanisms of tissue storage and the production of erythrocytes **(Fisher & Nemeth, 2017).**

Once iron enters the enterocyte, it may be stored as ferritin or transferred into circulation by ferroportin, which crosses the basolateral membrane. Apoferritin, the variant of ferritin devoid of iron, exhibits inherent catalytic properties that convert ferrous iron into ferric iron, thereby promoting its binding and subsequent storage as ferritin **(Ems et al., 2023).**

Ferroportin and Hepcidin Interactions

Hepcidin controls iron efflux from cells via two well-established mechanisms: first, by preventing ferroportin from adopting an open-outward conformation; and second, by inducing endocytosis and destruction of ferroportin **(Nemeth et al., 2004).** The occlusion mechanism operates efficiently at hepcidin concentrations that maintain the majority of ferroportin molecules in an occluded state for prolonged durations, and it can be promptly reversed with a decrease in hepcidin levels. The process of endocytosis may begin when hepcidin briefly interacts with ferroportin, which causes ferroportin to be permanently removed from the cell surface. In order to restore iron transport, ferroportin must be synthesized again. We anticipate that the second mechanism will become active at lower hepcidin concentrations and will continue to exert its influence even after hepcidin levels fall **(Aschemeyer et al., 2018).**

Total iron storage, bone marrow red blood cell generation, blood hemoglobin concentration, and blood oxygen content are all interconnected elements that affect the rate of iron absorption in humans.During periods of inflammation, the body exhibits reduced iron absorption to limit bacterial access to this essential nutrient. Recent findings indicate that the regulation of ferroportin by hepcidin is a key factor in the syndrome of anemia of chronic disease **(Piskin, 2022).**

The function of hepcidin in IDA pathogenesis and diagnosis

The bactericidal capabilities of hepcidin, a liver protein, were first discovered as a cysteine-rich urine antimicrobial peptide. Research has shown that hepcidin, an essential protein for iron homeostasis in iron storage disorder knockout models, is dramatically overexpressed in iron-overloaded mice **(D'Angelo, 2013).**

Hepcidin production is mostly carried out by hepatocytes at the cellular level. A precursor to hepcidin, a preprohormone of 84 amino acids, is initially synthesized. The molecule is first hydrolyzed into prohormone and then further cleaved to produce hepcidin. The fully developed hepcidin protein is comprised of 25 amino acids. A multitude of factors influence the expression of the hepcidin gene **(Chambers, 2024).**

Up-regulation takes place during inflammatory conditions and is chiefly driven by IL-6, a pro-inflammatory cytokine secreted by diverse cell types. Transferrin, a protein

responsible for binding iron in the bloodstream, has the capacity to stimulate the production of hepcidin. This suggests that there is an adequate storage of iron in the serum, indicating that the mobilization of iron from intracellular reserves is not required at this time **(Chambers, 2024).**

Function of Hepcidin

When hepcidin is released from hepatocytes, it interacts with ferroportin-1 to affect plasma iron levels. The lysosomal breakdown of the hepcidin-ferroportin complex is the next step after ferroportin and hepcidin interact. This interaction predominantly influences duodenal enterocytes and reticuloendothelial macrophages **(Chambers, 2024).**

Important roles are played by duodenal enterocytes in iron absorption from food and by reticuloendothelial macrophages in the storage of iron from erythrocyte breakdown in the liver, spleen, and bone marrow. When ferroportin isn't working properly, enterocytes can't absorb iron and macrophages can't release iron **(Chambers, 2024).**
Hepcidin plays a significant role in innate immunity through its interactions with IL-6 and a range of pro-inflammatory cytokines. The confinement of iron within cellular structures to restrict its accessibility for pathogenic or neoplastic proliferation is predominantly governed by the stimulation of hepcidin through IL-6. This inherent mechanism may offer safeguarding against a range of pathogens, including streptococcal and malarial species **(Elmore & Ellis, 2022).**

Serum hepcidin is involved in the process of fighting against infections; consequently, serum hepcidin levels may be affected by inflammation. Inflammatory conditions, including preeclampsia, malaria, and obesity, can modify hepcidin levels and lead to iron restriction. Considering all contributing clinical factors is essential for diagnosing anemia and determining individualized treatment **(Elmore & Ellis, 2022).**

The Hepcidin-Ferroportin Axis and Its Role in Internal Defense

Hepcidin production is stimulated by infections and inflammations, mostly due to the effects of the cytokine interleukin-6 (IL-6). Low iron levels in plasma and extracellular fluid, or hypoferremia, result from elevated hepcidin levels, which in turn inhibit ferroportin action. In addition to hepcidin, microbes that bind to toll-like receptors inhibit cellular ferroportin mRNA transcription **(Guida et al., 2015).**

It is adequate to provoke hypoferremia; however, the degree to which this phenomenon influences hypoferremia in the context of in vivo infections is still ambiguous. Ferroportin appears to have emerged earlier than hepcidin in the evolutionary sequence, suggesting that studies that examine the hypoferremic effects of infection and inflammation in invertebrates, who do not have hepcidin, might provide valuable information **(Nemeth et al., 2004).**

Infections result in increased cytokine levels that inhibit erythropoiesis while enhancing the generation of myeloid cells crucial for host defense **(Weiss et al., 2019).**

Infections promote the recycling of damaged erythrocytes and other cellular components, which decreases plasma iron usage, but suppresses erythropoiesis, which increases plasma iron availability. The disparity would enhance transferrin saturation with iron and stimulate the synthesis of nontransferrin-bound iron (NTBI), thereby heightening the likelihood of microbial proliferation. The inflammatory increase in hepcidin, along with the influence of inflammation on ferroportin transcription, restricts the generation of non-transferrin bound iron (NTBI) by sequestering iron predominantly within macrophages. The concept of "nutritional immunity" holds particular importance in the context of infections induced by gram-negative bacteria and specific fungi **(Stefanova et al., 2017).**

Hepcidin Regulation

The maintenance of hepcidin homeostasis is largely influenced by iron. When iron stores and plasma iron levels are high, the liver produces hepcidin, which limits the body's ability to absorb iron from food and store it. The body's ability to regulate iron and hepcidin levels is crucial for maintaining healthy blood iron levels; when iron insufficiency occurs, hepcidin production drops **(D'Angelo, 2013).**

When iron levels rise over the typical limits of 65–175 mcg/dL for men and 50–170 mcg/dL for women, hepcidin production is increased **(Chambers et al., 2024).**

Because of its high iron requirement, the erythropoietic process controls hepcidin synthesis. Simultaneously improving intestinal iron absorption, hepcidin suppression causes hepatocytes and macrophages to release stored iron. This condition requires iron supplementation for the synthesis of hemoglobin. Hepcidin levels increase in response to inflammation and infection. Hypoferremia and anemia associated with inflammatory disorders, symptoms of iron dysregulation, may ensue. One possible role of hypoferremia in host defense is to reduce the amount of iron that microbes may use **(Ganz, 2006).**

Hepcidin and erythropoiesis

Hepcidin levels are drastically decreased by increased erythropoietic activity.. A solitary administration of erythropoietin (EPO) within a 24-hour period markedly reduces hepcidin levels in humans **(Ashby et al., 2010).**
In cases of ineffective erythropoiesis, erythroblasts synthesize two proteins: growth differentiation factor 15 (GDF15) and twisted gastrulation I (TWSG1), both of which play a role in the mediation of hepcidin suppression (Grootendorst et al., 2021). EPO influences iron homeostasis in an indirect manner. The production of EPO in reaction to hypoxic stimuli promotes the appropriate expansion of the erythron while simultaneously averting the risk of excessive erythropoiesis. The release of GDF15 and TWSG1 results in the inhibition of hepcidin synthesis, as previously observed

(Grootendorst et al., 2021).
An increase in red blood cell hemoglobin synthesis—which requires an appropriate supply of iron—is triggered by the first response to acute hypoxia, which is the beginning of erythropoietin (EPO). If hepcidin is downregulated, the erythroid lineage's production and hemoglobinization might progress **(D'Angelo, 2013).**

Hepcidin and inflammation

The etiology of acute inflammation is multifaceted, and the fundamental pathophysiological processes continue to be the subject of ongoing research. The longevity of erythrocytes is diminished, in part due to the activation of macrophages by inflammatory cytokines, with hemolysis possibly contributing to this phenomenon. When it comes to erythropoiesis, inflammatory cytokines are bad news. They reduce erythropoietin synthesis and effectiveness and block the growth and differentiation of erythroid progenitor cells. There is less iron available for erythropoiesis when inflammation increases hepcidin synthesis and inhibits ferroportin, two hormones that regulate iron levels **(Wang & Babitt, 2016).**

Iron concentrations do not regulate hepcidin production in inflammatory conditions.; rather, it is heightened as a result of stimulation by IL-6 **(Weiss et al., 2019).**

Hepcidin excess ; Hereditary Hemochromatosis

Decreased hepcidin production results from an autosomal recessive gene imperfection. HFE mutations exhibit a higher prevalence among individuals of European descent. Reduced hepcidin levels lead to enhanced dietary iron absorption and increased iron release from macrophages **(Chambers et al., 2024).**

Persistent iron absorption in the presence of sufficient serum levels may result in iron overload, defined as total body iron exceeding 20 grams. Hemochromatosis symptoms arise from iron accumulation in body tissues and generally manifest in men during the fourth decade of life and in women during the fifth **(Porter & Rawla, 2024).**

Hyperpigmentation of the skin, cirrhosis of the liver, and diabetes mellitus make up the traditional trio. Hypogonadism, arthropathy, hypothyroidism, and dilated cardiomyopathy are among the other findings.. Individuals diagnosed with hemochromatosis demonstrate an increased susceptibility to infections, attributed to the persistent elevation of serum iron levels during inflammatory conditions **(Porter & Rawla, 2024).**
The diagnostic criteria encompass iron panel results that reveal elevated serum iron levels, heightened ferritin (> 200 mcg/L), and transferrin saturation levels surpassing 45%. The approach to treatment encompasses alterations in lifestyle, therapeutic phlebotomy, and the application of pharmacological interventions **(VanWagner & Green, 2014).**

The Relation between Anemia and Hepcidin

Hepcidin and anemia

1. Iron deficiency anemia

Pure iron deficiency anemia is characterized by drastically decreased hepcidin levels in blood and urine, which might be difficult, if not impossible, to diagnose with current methods. Low levels of transcriptional activation by iron and active suppression by erythroid factors are likely to blame for the reduced expression. Even when anemia is not present, hepcidin seems to be a sensitive indicator of iron deficiency. Symptoms of low hematocrit or hemoglobin include decreased hepcidin, serum ferritin, and transferrin saturation **(Ganz et al., 2008).**

2. Iron-refractory iron deficiency anemia (IRIDA)

Failure to achieve a hemoglobin increase of less than 1 g/dl after 4 weeks of oral iron therapy is referred to as refractoriness, assuming acceptable patient compliance and exclusion of acquired gastrointestinal diseases **(Hershko et al., 2014).**

IRIDA is a recessive genetic anemia that develops when the TMPRSS6 gene, which codes for matriptase-2, is mutated. This serine protease acts across membranes to prevent the production of hepcidin, an essential iron regulator that lowers intestinal iron absorption.

The biochemical analysis reveals hepcidin levels that are within the normal to elevated range, accompanied by inadequate transferrin saturation and the presence of microcytic hypochromic anemia. Anaemia frequently manifests in the postnatal period, though it can be identified subsequently. The effectiveness of oral iron therapy could be affected by the degree of mutation in the TMPRSS6 gene. Other pharmaceutical treatments for anemia include anti-hepcidin antibodies, liposomal oral iron therapy, intravenous iron infusions, and others **(Abd-Elmawgood et al., 2024).** Heteromeric SMAD complexes control hepcidin production by starting transcription of the Hamp gene after nuclear translocation. By competing with membrane-bound HJV (m-HJV) for BMP ligands, soluble HJV (s-HJV) inhibits hepcidin transcription and hence the BMP pathway. Anemia develops because matriptase-2 mutations raise hepcidin levels, which in turn prevent iron absorption over time **(Ramsay et al., 2009).**

3. Anemia with iron overload

Iron builds up in people with β-thalassemia and congenital dyserythropoietic anemia, indicating the existence of anemia. Individuals who do not undergo transfusions exhibit markedly lower levels of hepcidin in both serum and urine. The heightened erythropoietic activity, coupled with the lack of hepcidin modulation due to iron overload, obstructs the signaling pathway responsible for hepcidin synthesis. In disorders characterized by inefficient erythropoiesis, the modulation of hepcidin synthesis is influenced by GDF15 and TWSG1 **(D'Angelo, 2013).**

In patients who undergo chronic transfusions, hepcidin levels are markedly increased in contrast to those who do not receive transfusions, a phenomenon attributable to iron overload and suboptimal erythropoiesis. People who suffer from thalassemia yet do not get blood transfusions, iron is stored in hepatocytes instead of macrophages, resembling the situation observed in those who are transfused. The consequence of this modified distribution of iron within cells is that serum ferritin concentrations are significantly reduced in individuals who have not received transfusions, failing to provide an accurate reflection of hepatic iron reserves **(D'Angelo, 2013).**

4. Chronic illness and inflammation anemia

Mixed anemia can manifest in chronic inflammatory conditions that are marked by bleeding and/or nutritional deficiencies. In this context, hyposideremia may alleviate the increase in hepcidin levels prompted by inflammation. A true iron deficiency resulting from non-intestinal absorption influenced by hepcidin can occur when inflammation endures over an extended period **(D'Angelo, 2013).**

Table 1 ; Hepcidin levels and other iron-related parameters in various types of anemia **(Cui et al., 2009) .**

Type of anemia	**Hepcidin level**	**Transferrin saturation**	**Ferritin**	**Soluble transferrin receptor**
Iron deficiency anemia	Low	Low	Low	Increased
Iron refractory iron dificency anemia	High	Low	Low	Variable
Anemia with iron over load	Low (not transfused	High	High	Variable
Anemia with chronic disease	High	Low	Normal or high	Normal
Mixed anemia	Normal	Low	Normal or high	Normal or high
Anemia in chronic kidney disease	High	Variable	Variable	Variable
Resistant to erythropoietin	High	Variable	Variable	Variable

The duration of a pregnancy's second and third trimesters, there is a reduction in maternal hepcidin levels, which serves to promote increased iron transfer through the placenta (Sangkhae et al., 2020).

The exact mechanism underlying this inhibition remains insufficiently comprehended. The administration of iron supplementation has raised apprehensions regarding the potential for iron overload during pregnancy, which could jeopardize fetal development. Recent investigations reveal that, even in the context of prenatal

reduction, maternal hepcidin persists in its role of controlling the amount of iron that the placenta can absorb, thereby safeguarding the fetus against iron overload **(Georgieff, 2019).**

During pregnancy, the processes that control the transfer of iron from the mother to the fetus

are not fully elucidated, especially concerning the respective roles of maternal, placental, and fetal signals in maintaining iron homeostasis for both the fetus and the mother. In the course of a healthy pregnancy, hepcidin levels exhibit an increase during the first trimester, then a sharp drop to almost undetectable levels in the second and third trimesters that follow. The suppression of maternal hepcidin plays a crucial role in enhancing iron availability, thereby promoting the efficient transport of iron from the mother's bloodstream to the developing baby via ferroportin and TfR1. The physiological mechanism underlying the suppression of maternal hepcidin during pregnancy has yet to be elucidated **(Albertine et al., 2021).**

Table 2 ; Criteria for the identification of various forms of inflammatory anemia **(Petzer et al., 2018).**

Marker	**Anemia of inflammation**	**Anemia of inflammation plus iron deficiency anemia**	**Limitations \ comments**
Bone marrow iron staining	Normal - elevated	Normal - reduced	• Gold standerd • Invasive method , not routinely used
Serum iron	Low	Low	Underlies diurnal variations
Ferritin	Elevated	Reduced-normal-elevated	• Most commonly used marker • Ferritin is an acute phase protein and doesn't accurately reflect iron status during inflammation • Ferritin < 30 ng\ml always associated with true iron deficiency
Transferrin	Normal- reduced	Normal- high	
Tf-Sat	Low	Low	Dependent on iron and transferrin level
STfR	Normal - elevated	Elevated	• Good marker for need of iron for erythropoiesis In absence of inflammation • Values affected by inflammation and ESA application
sTfR\ log ferritin	Normal	Elevated	Used for differentiation , but there is a lack of a prospective study
Hepcidin	Elevated	Normal- reduced	• Expression is more affected b iron deficiency (suppressing) than by

			inflammation • Not standard • Weak correlations with CKD patients • Possible predictive parameter for success of iron and\or ESA treatment
MCV\MCH	Normal	Normal- reduced	If reduced indication of iron deficiency anemia
Reticulocyte Hb content	Normal- reduced	Reduced	Indicate insufficient iron availability for erythropoiesis
CRP	Increased	Increased	• NON specific inflammatory maker • Iron independent parameter • Correlation with severity of anemia
IL 6	Increased	Increased	• NON specific inflammatory maker • Iron independent parameter
Hypochromic RBCs	Normal	Normal - elevated	• Related to MCV as a sensitive marker for iron availability for erythroid progenitors

Conclusion & recommendations

Iron deficiency anemia (IDA) continues to pose a considerable challenge to global health, especially affecting at-risk populations including infants, children, and pregnant women. The fetal-neonatal period holds significant importance, as iron is essential for proper brain development

, erythropoiesis, and cellular metabolism.

The maternal–fetal iron axis is tightly regulated by multiple factors, with hepcidin emerging as the central regulatory hormone. Hepcidin controls iron absorption and distribution through its interaction with ferroportin and is responsive to iron status, erythropoietic activity, inflammation, and hypoxia.

During pregnancy, maternal hepcidin levels are physiologically suppressed in order to improve the fetal iron transport, particularly during the third trimester. Disruptions in this regulatory mechanism due to inflammation, infection, or chronic disease can impair fetal iron acquisition and lead to neonatal iron deficiency. Umbilical cord hepcidin has shown promise as a non-invasive biomarker reflecting fetal iron status and maternal-fetal iron transport dynamics.Our review highlight the importance of Use of Hepcidin as a Biomarker Promote further research to standardize hepcidin assays and validate its use as a reliable marker for identifying fetal and neonatal iron deficiency, particularly through umbilical cord blood analysis and Develop accessible, affordable, and field-friendly diagnostic tools for hepcidin and related iron markers to improve early detection in resource-limited settings.

References:

Abd-Elmawgood, E. A., Hassan, M. H., Mobark, D. H., & Rashwan, N. I. (2024). Iron Refractory Iron Deficiency Anemia. SVU-International Journal of Medical Sciences, 7(2), 9-17.

Albertine E . Donker , Hilde van der Staaij , Dorine W. Swinkels , (2021) . The critical roles of iron during the journey from fetus to adolescent: Developmental aspects of iron homeostasis,Blood Reviews,Volume 50 ,100866,ISSN 0268-960X,

Aschemeyer, S.; Qiao, B.; Stefanova, D.; Valore, E.V.; Sek, A.C.; Ruwe, T.A.; Vieth, K.R.; Jung, G.; Casu, C.; Rivella, S.; (2018) . Structure-function analysis of ferroportin defines the binding site and an alternative mechanism of action of hepcidin. Blood, 131, 899–910.

Ashby DR, Gale DP, Busbridge M, (2010) . Erythropoietin administration in humans causes a marked and prolonged reduction in circulating hepcidin. Haematologica ; 95 : 505 - 8.

Black M.M., Walker S.P., Fernald L.C.H., Andersen C.T., DiGirolamo A.M., Lu C., McCoy D.C., Fink G., Shawar Y.R., Shiffman J., (2017) . Early childhood development coming of age: Science through the life course. Lancet. 2017 ; 389 : 7790.

Camaschella C. Iron - deficiency anemia . N Engl J Med . (2015) .; 372 (19):1832-1843.

Campbell, R. K., Buhimschi, C. S., Zhao, G., Dela Rosa, C., Stetson, B. T., Backes, C. H., & Buhimschi, I. A. (2022) . Prevalence of and Risk Factors for Iron Deficiency in Twin and Singleton Newborns. Nutrients, 14(18), 3854.

Ceulemans M, Van de Vel J, Swinkels DW, Laarakkers CMM, Billen J, Van Calsteren K, Allegaert K .(2023) . Hepcidin Status in Cord Blood : Observational Data from a Tertiary Institution in Belgium. Nutrients. 2023 Jan 20;15(3):546.

Chambers K, Ashraf MA, Sharma S. Physiology, Hepcidin. [Updated 2023 Apr 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-Available from: https://www.ncbi.nlm.nih.gov/books/NBK538257/

Cui, Y., Wu, Q., & Zhou, Y. (2009). Iron-refractory iron deficiency anemia : new molecular mechanisms. Kidney international, 76(11), 1137–1141.

D'Angelo, G. (2013). Role of hepcidin in the pathophysiology and diagnosis of anemia. In Blood Research (Vol. 48, Issue 1, pp. 10–15).

DeLoughery TG.(2019) . Safety of Oral and Intravenous Iron . Acta Haematol . ;142(1):8-12.

Elghetany MT, Banki K. (2022) . Erythrocytic disorders . In : McPherson RA , Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Philadelphia, PA: Elsevier; 2022:chap 33.

Elmore, C., & Ellis, J. (2022) . Screening , Treatment , and Monitoring of Iron Deficiency Anemia in Pregnancy and Postpartum. In Journal of Midwifery and Women's Health (Vol. 67, Issue 3, pp. 321–331). John Wiley and Sons Inc.

Ems, T., St Lucia , K., & Huecker, M. R. (2023). Biochemistry, Iron Absorption. In *StatPearls*. StatPearls Publishing. Available from: https://www.ncbi.nlm.nih.gov/books/NBK448204/

Fisher AL, Nemeth E. (2017) . Iron homeostasis during pregnancy. Am J Clin Nutr. ;106(6):1567S-1574S.

Gallagher P. G. (2022). Anemia in the pediatric patient. Blood, 140(6),571 – 593.

Ganz T.(2006) . Molecular pathogenesis of anemia of chronic disease . Pediatr Blood Cancer ;46:554-7.

Ganz T. (2019) . Anemia of inflammation . N Engl J Med. 2019;381(12):1148-1157.

Ganz, T., Olbina, G., Girelli, D., Nemeth, E., & Westerman , M. (2008) . Immunoassay for human serum hepcidin. Blood, 112(10), 4292–4297.

Georgieff, M. K., Krebs, N. F., & Cusick, S. E. (2019). The benefits and risks of iron supplementation in pregnancy and childhood. Annual Review of Nutrition, 39, 121–146.

Grootendorst, S., de Wilde, J., van Dooijeweert, B., van Vuren, A., van Solinge, W., Schutgens, R., van Wijk, R., & Bartels, M. (2021) . The Interplay between Drivers of Erythropoiesis and Iron Homeostasis in Rare Hereditary Anemias: Tipping the Balance. International Journal of Molecular Sciences, 22(4), 2204.

Guida, C., Altamura, S., Klein, F. A., Galy, B., Boutros, M., Ulmer, A. J., Hentze, M. W., & Muckenthaler, M. U. (2015). A novel inflammatory pathway mediating rapid hepcidin-independent hypoferremia. Blood, 125(14), 2265–2275.

Hershko, C., & Camaschella, C. (2014). How I treat unexplained refractory iron deficiency anemia. Blood, 123(3), 326–333.

McCann S, Perapoch Amadó M, Moore SE. (2020) . The Role of iron in brain development: a systematic review. Nutrients. 2020;12(7):2001.

Means, R. T. (2020). Iron deficiency and iron deficiency anemia: Implications and impact in pregnancy, fetal development, and early childhood parameters. In Nutrients (Vol. 12, Issue 2) 447. MDPI AG.

Nemeth, E.; Tuttle, M.S.; Powelson, J.; Vaughn, M.B.; Donovan, A.;Ward, D.M.; Ganz, T.; Kaplan, J.(2004) . Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. Science 2004, 306, 2090–2093.

Petzer, Verena & Theurl, Igor & Weiss , Guenter . (2018) . Established and Emerging Concepts to Treat Imbalances of Iron Homeostasis in Inflammatory Diseases.Pharmaceuticals. 11. 135. 10.3390/ph11040135.

Piskin, E., Cianciosi, D., Gulec, S., Tomas, M., & Capanoglu, E. (2022) . Iron Absorption: Factors, Limitations, and Improvement Methods. ACS omega,7(24),20441–20456.

Porter JL, Rawla P. Hemochromatosis . [Updated 2024 Oct 6] . In : StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing ; 2024 Jan - . : NBK430862 PMID: 28613612 https://www.ncbi.nlm.nih.gov/books/NBK430862/

Ramsay AJ, Hooper JD, Folgueras AR, Velasco G, Lopez-Otin C. Matriptase-2 (TMPRSS6): (2009) . a proteolytic regulator of iron homeostasis. Haematologica ;94:840-9.

Rosich del Cacho,. Mozo del Castillo,. (2021) . Anemia . Classification and diagnosis, Pediatr Integral 2021; XXV (5): 214 – 221

Sangkhae V, Fisher AL, Wong S, Koenig MD, Tussing-Humphreys L, Chu A, Lelić M, Ganz T, Nemeth E. (2020) . Effects of maternal iron status on placental and fetal iron homeostasis. J Clin Invest. 2020 Feb 3;130(2):625-640 .PMID: 31661462; PMCID: PMC6994143.

Shadid,N. ., (2018). Iron Storage : Ferritin. LibreTexts . Saint Mary's College in Notre Dame.

Stefanova, D.; Raychev, A.; Arezes, J.; Ruchala, P.; Gabayan, V.; Skurnik, M.; Dillon, B.J.; Horwitz, M.A.; Ganz, T.; Bulut, Y.; (2017) . Endogenous hepcidin and its agonist mediate resistance to selected infections by clearing non-transferrin-bound iron. Blood 2017, 130, 245–257.

VanWagner LB, Green RM. (2014) . Elevated serum ferritin . JAMA . 2014 Aug 20;312(7):743-4. PMID: 25138336; PMCID: PMC4424930.

Wang CY, Babitt JL.(2016). Hepcidin regulation in the anemia of inflammation. Curr Opin Hematol. 2016 May;23(3):189-97. doi: 10.1097/MOH.0000000000000236. PMID: 26886082; PMCID: PMC4993159.

Weiss G, Ganz T, Goodnough LT . (2019) . Anemia of inflammation . Blood . 2019 Jan 3;133(1):40-50. Epub 2018 Nov 6. PMID: 30401705; PMCID: PMC6536698.

Zierk J, Hirschmann J, Toddenroth D,. (2019) . Next - generation reference intervals for pediatric hematology. Clin Chem Lab Med. 2019;57(10):1595-1607.