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Hepcidin as the Central Regulator in Pregnancy-Associated Iron Deficiency Anemia and Vitamin D Deficiency

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Abstract: Iron deficiency anemia (IDA) and vitamin D deficiency are among the most prevalent micronutrient deficiencies worldwide, particularly affecting pregnant women. The physiological demands for both iron and vitamin D increase significantly during pregnancy to support maternal health, fetal development, and placental function. Failure to meet these demands leads to adverse outcomes, including preterm birth, low birth weight, preeclampsia, and maternal infections. Hepcidin, a liver-derived peptide hormone, is central to systemic iron regulation. It modulates dietary iron absorption and mobilization from body stores through its interaction with ferroportin. In healthy pregnancy, hepcidin levels are physiologically suppressed to enhance iron bioavailability. However, inflammation or vitamin D deficiency may elevate hepcidin levels, exacerbating IDA and complicating its management. Vitamin D, primarily recognized for its role in calcium metabolism, is also a key regulator of hepcidin expression. Through receptor-mediated pathways, vitamin D suppresses hepcidin synthesis, improving iron absorption and mobilization. The coexistence of IDA and vitamin D deficiency during pregnancy creates a complex clinical scenario, compounded by overlapping risk factors like poor diet, limited sun exposure, and chronic inflammation. Emerging evidence highlights hepcidin as a dynamic biomarker capable of differentiating IDA from anemia of inflammation. This review explores the intricate relationship between vitamin D deficiency and IDA, with a focus on hepcidin as both a regulator and biomarker. We discuss physiological and pathological mechanisms, diagnostic applications of hepcidin, and therapeutic opportunities, including the synergistic role of vitamin D and iron supplementation. By addressing the dual burden of vitamin D deficiency and IDA, this review provides a comprehensive framework for improving maternal and neonatal outcomes through targeted interventions and biomarker-guided therapies. Future research should focus on refining diagnostic tools and exploring innovative therapies to optimize anemia management in pregnancy.

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Introduction

Iron deficiency anemia (IDA) and vitamin D deficiency are two of the most prevalent micronutrient deficiencies worldwide, particularly affecting pregnant women [1]. During pregnancy, the physiological demands for iron and vitamin D increase substantially to support maternal health, fetal development, and placental function. Failure to meet these increased requirements can result in adverse maternal and neonatal outcomes, including preterm birth, low birth weight, preeclampsia, and increased susceptibility to infections [2]. Despite global efforts to address these deficiencies, they remain significant public health challenges, especially in resource-limited settings [3].

IDA affects an estimated 36% of pregnant women globally and is characterized by insufficient iron to meet the needs for erythropoiesis, leading to reduced hemoglobin levels and impaired oxygen delivery to tissues. Pregnancy imposes a unique iron burden due to the growing fetal and placental demands, the expansion of maternal red blood cell mass, and losses associated with delivery. The pathophysiology of IDA is often exacerbated by dietary inadequacies, infections, and underlying chronic inflammatory conditions. These factors can lead to dysregulation of iron homeostasis, where hepcidin, a liver-derived peptide hormone, plays a central role [4].

Hepcidin regulates systemic iron metabolism by controlling dietary iron absorption and mobilization from body stores. It achieves this by binding to and promoting the degradation of ferroportin, the sole iron exporter on enterocytes, macrophages, and hepatocytes. In healthy pregnancy, hepcidin levels are physiologically suppressed to accommodate increased iron demands. However, elevated hepcidin levels in response to inflammation or infection can impair iron absorption and utilization, complicating the management of IDA in these scenarios. This interplay underscores the importance of hepcidin not only as a regulator of iron homeostasis but also as a biomarker for differentiating iron deficiency from anemia of inflammation [5].

Vitamin D deficiency, affecting an estimated 40–98% of pregnant women worldwide, also poses significant health risks. Vitamin D, primarily known for its role in calcium and phosphate metabolism, is increasingly recognized for its broader physiological functions, including immunomodulation and regulation of inflammation. Emerging evidence suggests that vitamin D deficiency may exacerbate IDA by influencing hepcidin expression. Vitamin D suppresses hepcidin synthesis through its receptor-mediated pathways, enhancing dietary iron absorption and mobilization from stores. Thus, vitamin D deficiency may contribute to the persistence of IDA by failing to modulate hepcidin appropriately [6].

The coexistence of vitamin D deficiency and IDA during pregnancy creates a complex clinical scenario. Both conditions share overlapping risk factors, including poor dietary intake, limited sun exposure, and increased physiological demands. Moreover, chronic inflammation, a common feature in conditions such as obesity, infections, and autoimmune diseases, further complicates the regulation of hepcidin, impairing iron and vitamin D metabolism [7]. Understanding the interconnections between these conditions is critical for developing effective diagnostic and therapeutic strategies.

Recent advances in our understanding of hepcidin's role in iron metabolism and its modulation by vitamin D have opened new avenues for research and clinical application. Hepcidin has emerged as a dynamic biomarker that can differentiate between iron deficiency and anemia of inflammation, addressing the limitations of traditional markers like ferritin and hemoglobin [8]. Furthermore, interventions targeting hepcidin regulation, such as vitamin D supplementation, offer promising strategies for improving iron status and addressing anemia in pregnant women [9].

This review aims to explore the intricate relationship between vitamin D deficiency and IDA in pregnancy, focusing on the central role of hepcidin as both a regulator and biomarker. We will examine the physiological and pathological mechanisms linking these conditions, discuss the diagnostic utility of hepcidin, and highlight therapeutic opportunities that leverage vitamin D's effects on hepcidin regulation.

The Role of Hepcidin in Iron Regulation and Its Modulation by Vitamin D

Hepcidin as a Regulator of Iron Homeostasis

Hepcidin, a small peptide hormone produced primarily in the liver, is central to systemic iron regulation. Its role is to maintain the balance between iron absorption, utilization, and storage. This regulation is critical because while iron is essential for vital processes such as oxygen transport, DNA synthesis, and energy metabolism; excess iron can generate free radicals and cause oxidative stress, leading to cellular damage. Hepcidin achieves this balance by modulating the activity of ferroportin, the only known cellular iron exporter [10].

Mechanism of Action

Hepcidin acts by binding to ferroportin, which is expressed on the surface of cells involved in iron metabolism, including enterocytes in the duodenum (responsible for dietary iron absorption), macrophages (responsible for recycling iron from senescent red blood cells), and hepatocytes (which store iron). Upon binding, hepcidin triggers the internalization and degradation of ferroportin, effectively halting iron export from these cells into the bloodstream. By regulating ferroportin activity, hepcidin determines how much dietary iron is absorbed and how much stored iron is mobilized, ensuring that plasma iron levels remain within a physiological range [11].

Regulation of Hepcidin Expression

Hepcidin synthesis is tightly regulated by several factors that ensure the maintenance of iron homeostasis in response to physiological and pathological conditions. Elevated iron levels in the plasma or liver stimulate hepcidin expression through the BMP/SMAD signaling pathway. This regulatory mechanism prevents excessive iron absorption, thereby protecting against iron overload disorders such as hereditary hemochromatosis [12]. Conversely, increased erythropoietic demand, associated with heightened red blood cell production, suppresses hepcidin synthesis. This suppression is mediated by erythroferrone, a hormone secreted by erythroblasts during erythropoiesis, enabling enhanced iron absorption and mobilization to meet the increased demand [13]. Inflammation also plays a pivotal role in modulating hepcidin levels; inflammatory cytokines, particularly interleukin-6 (IL-6), significantly upregulate hepcidin production via the JAK/STAT pathway. This response forms part of the body's defense system, limiting iron availability to pathogens during infection, but it also contributes to anemia of inflammation (AI) [14]. Lastly, hypoxia, or low oxygen levels, suppresses hepcidin expression to promote iron mobilization and support erythropoiesis under conditions of anemia or oxygen deprivation [15].

Hepcidin's Role in Physiological Iron Homeostasis

Hepcidin plays a critical role in maintaining iron homeostasis by aligning iron supply with the body's physiological needs. In states of iron sufficiency or overload, elevated hepcidin levels inhibit iron absorption by reducing the activity of ferroportin, the iron-exporting protein, in intestinal enterocytes. This mechanism effectively limits dietary iron uptake and prevents excessive iron accumulation [16]. Conversely, in conditions of iron deficiency or anemia, hepcidin levels are suppressed, which enhances ferroportin activity and promotes increased dietary iron absorption to restore iron balance. Hepcidin also regulates iron mobilization from macrophages, which recycle iron from senescent red blood cells. Under conditions of iron sufficiency, hepcidin inhibits excessive iron release from these macrophages. In contrast, during iron deficiency, the suppression of hepcidin ensures efficient mobilization of stored iron to support the body's needs [10].

Hepcidin Dysregulation: Pathological Implications

Dysregulation of hepcidin is associated with several pathological conditions that impact iron homeostasis. In iron deficiency anemia (IDA), hepcidin levels are typically suppressed to optimize iron absorption and mobilization. Despite this adaptive response, inadequate dietary iron intake or impaired absorption can still lead to IDA, particularly in high-demand states such as pregnancy [16]. Anemia of inflammation (AI), on the other hand, is characterized by elevated hepcidin levels during chronic inflammation or infection. This increase restricts iron availability by promoting its sequestration within macrophages and reducing dietary iron absorption, resulting in functional iron deficiency despite adequate iron stores [17]. Additionally, iron overload disorders, such as hereditary hemochromatosis, are linked to mutations in the genes that regulate hepcidin expression. These mutations cause abnormally low hepcidin levels, leading to excessive iron absorption and accumulation in body tissues [18].

Hepcidin Dynamics During Pregnancy

Hepcidin regulation during pregnancy undergoes significant adaptations to meet the increased physiological demands for iron. These changes are crucial for supporting maternal health, fetal development, and placental growth. The total iron requirement during pregnancy is approximately 1,000 mg, distributed across the expansion of maternal red blood cell mass, the needs of the growing fetus, and the iron requirements of the placenta. To meet these demands, systemic hepcidin levels are dynamically regulated throughout pregnancy [2].

Hepcidin Suppression: A Physiological Adaptation

Pregnancy is associated with a progressive suppression of hepcidin levels, particularly during the second and third trimesters when fetal growth and erythropoiesis are at their peak. This physiological adaptation facilitates enhanced iron absorption and mobilization to meet the increased demands of pregnancy [5]. Suppressed hepcidin levels allow ferroportin to remain active on enterocytes, significantly increasing dietary iron absorption. Studies have shown that iron absorption capacity rises by 50–70% during the second trimester compared to non-pregnant states. Furthermore, hepcidin suppression promotes the release of stored iron from hepatocytes and macrophages, ensuring an adequate supply of iron for maternal erythropoiesis and fetal development [19].

These trends are supported by research findings. For instance, a longitudinal study published in *Nutrients* documented a gradual decline in hepcidin levels throughout pregnancy, with the lowest concentrations observed during the third trimester. This decline was closely associated with increased serum transferrin saturation, indicating greater iron availability for both maternal and fetal needs [20].

Hepcidin Dysregulation in Pathological Conditions During Pregnancy

While physiological suppression of hepcidin supports iron demands during normal pregnancy, several pathological conditions disrupt this balance, leading to impaired iron absorption and mobilization. These disruptions can exacerbate iron deficiency anemia (IDA) and contribute to adverse maternal and fetal outcomes.

Preeclampsia is a pregnancy-specific disorder characterized by hypertension and systemic inflammation. Elevated inflammatory cytokines, particularly IL-6, stimulate hepcidin production via the JAK/STAT pathway. As a result, dietary iron absorption decreases, and stored iron remains sequestered in macrophages. Studies have reported significantly higher hepcidin levels in women with preeclampsia compared to those with uncomplicated pregnancies. This dysregulation contributes to maternal anemia and restricts placental iron transfer, increasing the risk of fetal growth restriction and low birth weight [21].

Maternal obesity is associated with chronic low-grade inflammation, characterized by elevated IL-6 and other pro-inflammatory markers. This inflammatory milieu leads to increased hepcidin expression, reducing iron bioavailability. Research has shown that obese pregnant women have higher hepcidin levels

and a higher prevalence of functional iron deficiency compared to non-obese counterparts, even when total iron stores are adequate. This dual burden of inflammation and iron dysregulation underscores the need for tailored interventions in this population [22].

Infections during pregnancy, whether acute or chronic, can exacerbate hepcidin elevation through the body's natural response to limit iron availability to pathogens (nutritional immunity). However, this protective mechanism inadvertently reduces iron availability for erythropoiesis, contributing to anemia of inflammation (AI) [14].

Emerging evidence suggests a link between GDM and hepcidin dysregulation. Women with GDM often exhibit mild systemic inflammation, which can elevate hepcidin levels and impair iron metabolism. These alterations may exacerbate IDA in this already high-risk group [23].

Impact of Dysregulated Hepcidin on Maternal and Fetal Outcomes

The consequences of hepcidin dysregulation during pregnancy extend beyond maternal health, significantly affecting fetal development and neonatal outcomes. Elevated maternal hepcidin levels can restrict placental iron transfer, resulting in fetal iron deficiency. This deficiency is linked to impaired neurodevelopment, lower birth weights, and an increased risk of neonatal anemia [24]. Furthermore, persistent maternal anemia, caused by inadequate iron absorption and mobilization due to elevated hepcidin levels, poses additional risks. These include a higher likelihood of preterm labor, postpartum hemorrhage, and maternal infections [25].

A study published in *Clinical Chemistry and Laboratory Medicine* found that pregnant women with elevated hepcidin levels were more likely to experience adverse outcomes, such as anemia and fetal growth restriction [26]. These findings underscore the importance of identifying and addressing the underlying causes of hepcidin dysregulation during pregnancy to improve maternal and neonatal health.

Vitamin D as a Modulator of Hepcidin

Vitamin D, traditionally recognized for its role in calcium and phosphate homeostasis, has emerged as a key regulator of systemic inflammation and iron metabolism. Its interaction with hepcidin, the master regulator of iron homeostasis, provides critical insights into the relationship between vitamin D deficiency and iron deficiency anemia (IDA) [6]. Vitamin D's ability to modulate hepcidin levels has significant implications for managing IDA during pregnancy, particularly in the context of chronic inflammation and heightened iron demands [9].

The Mechanism of Hepcidin Suppression by Vitamin D

Vitamin D exerts its regulatory effects on hepcidin through its active form, 1,25-dihydroxyvitamin D. This metabolite binds to the vitamin D receptor (VDR), which interacts with the promoter region of the hepcidin gene (HAMP) to suppress transcription. By reducing hepcidin expression, vitamin D increases the activity of ferroportin, the sole iron exporter on enterocytes, macrophages, and hepatocytes. This leads to enhanced dietary iron absorption and mobilization of stored iron [27].

Vitamin D plays a significant role in suppressing hepcidin levels through multiple mechanisms. One key pathway involves direct genomic interaction, where vitamin D-VDR complexes inhibit the transcription of the *HAMP* gene, effectively downregulating hepcidin synthesis [28]. Additionally, vitamin D exerts anti-inflammatory effects by reducing the production of pro-inflammatory cytokines, particularly interleukin-6 (IL-6). Since IL-6 is a potent stimulator of hepcidin expression via the JAK/STAT signaling pathway, vitamin D's ability to mitigate inflammation indirectly contributes to the suppression of hepcidin levels [29].

These dual mechanisms highlight the potential of vitamin D as a modulator of iron homeostasis, particularly in conditions characterized by hepcidin dysregulation. They also position vitamin D as a

potential therapeutic agent for addressing the dual burden of vitamin D deficiency and IDA, particularly in populations with inflammatory conditions.

Clinical Evidence Supporting Vitamin D's Role in Hepcidin Regulation

Numerous studies have explored the effects of vitamin D supplementation on hepcidin levels and iron metabolism, demonstrating its potential to improve iron status and mitigate anemia. Bacchetta et al. (2014) showed that a single high dose of vitamin D3 (300,000 IU) significantly reduced serum hepcidin concentrations within days of administration. This reduction was accompanied by improved markers of iron status, underscoring vitamin D's role in enhancing iron availability [27]. Similarly, Smith et al. (2015) found that vitamin D supplementation in pregnant women led to lower hepcidin levels and improved hemoglobin concentrations, particularly in those with concurrent vitamin D deficiency and iron deficiency anemia (IDA) [30]. Additionally, Zughaier et al. (2014) demonstrated that vitamin D inhibited hepcidin expression in monocytes exposed to inflammatory stimuli, highlighting its potential to alleviate anemia of inflammation (AI) in inflammatory conditions [6]. Collectively, these findings emphasize the ability of vitamin D to modulate hepcidin and improve iron status, making it a valuable intervention for managing IDA during pregnancy.

Vitamin D Deficiency and Hepcidin Dysregulation

Vitamin D deficiency is highly prevalent among pregnant women, with global estimates ranging from 40% to 98% depending on geographic and demographic factors. This deficiency exacerbates hepcidin dysregulation, leading to reduced dietary iron absorption and impaired mobilization from stores. Inflammatory conditions further amplify this effect, creating a vicious cycle that worsens anemia.
A systematic review by Lima et al. (2021) found that vitamin D deficiency was associated with a 61% increased risk of anemia in pregnant women, with hepcidin identified as a mediating factor. Another study observed that vitamin D supplementation in women with coexisting IDA and vitamin D deficiency significantly reduced hepcidin levels, improving iron parameters such as serum ferritin and transferrin saturation [31].

Vitamin D's Role in Pregnancy-Specific Conditions

The interaction between vitamin D and hepcidin is particularly significant during pregnancy, where vitamin D deficiency often coincides with increased inflammation and elevated hepcidin levels, contributing to impaired iron metabolism. In preeclampsia, women frequently exhibit low vitamin D levels alongside elevated hepcidin concentrations. Research indicates that vitamin D supplementation in these patients can reduce hepcidin expression, potentially enhancing iron availability and mitigating the risk of maternal and fetal complications [32]. Similarly, in gestational diabetes mellitus (GDM), elevated inflammatory markers contribute to increased hepcidin levels. The anti-inflammatory properties of vitamin D may help counteract this dysregulation, improving iron metabolism in affected women [33]. Maternal obesity presents another challenge, as it is associated with chronic low-grade inflammation and vitamin D deficiency, both of which drive hepcidin elevation. Addressing vitamin D deficiency in obese pregnant women may reduce hepcidin-mediated iron sequestration, thereby improving iron availability and overall maternal health [34].

Synergistic Effects of Vitamin D Deficiency and Elevated Hepcidin

Vitamin D deficiency and elevated hepcidin levels are distinct yet interconnected factors that significantly influence iron metabolism during pregnancy. When these conditions co-occur, their combined effects can exacerbate iron deficiency anemia (IDA), creating a self-reinforcing cycle. This section focuses on the unique interactions between these two factors and their implications for maternal and fetal outcomes.

The Feedback Loop Between Vitamin D Deficiency and Hepcidin

Vitamin D deficiency and hepcidin dysregulation are closely interconnected, forming a bidirectional relationship that establishes a feedback loop detrimental to iron metabolism. When vitamin D levels are reduced, the suppression of the *HAMP* gene, which encodes hepcidin, is impaired. This results in increased hepcidin production, which in turn limits iron absorption and release from stores, leading to functional iron deficiency [27]. Elevated hepcidin levels further exacerbate this cycle by inhibiting ferroportin activity, thereby restricting dietary iron absorption and iron mobilization from stores, compounding the effects of vitamin D deficiency [35].

This vicious cycle can significantly worsen iron deficiency anemia (IDA), particularly in populations with underlying inflammatory conditions or during high-risk pregnancies. These findings underscore the importance of targeted interventions to address both vitamin D deficiency and hepcidin dysregulation, breaking the cycle and improving iron availability in vulnerable populations.

Clinical Evidence of Synergy

Several studies have underscored the combined effects of vitamin D deficiency and elevated hepcidin on anemia and adverse pregnancy outcomes. For instance, a systematic review by Lima et al. (2021) found that pregnant women with vitamin D deficiency had a 61% higher risk of developing anemia, with hepcidin identified as a key mediator in this relationship. Furthermore, research has demonstrated the potential of high-dose vitamin D supplementation to mitigate these effects. Supplementation not only reduces hepcidin levels but also improves hemoglobin concentrations in women suffering from concurrent vitamin D deficiency and iron deficiency anemia (IDA) [31].

These findings highlight the critical importance of addressing both vitamin D deficiency and hepcidin dysregulation to optimize anemia management during pregnancy, ultimately improving maternal and fetal health outcomes.

Impact on Maternal and Fetal Outcomes

The combined impact of vitamin D deficiency and elevated hepcidin extends beyond maternal anemia, significantly affecting fetal development and outcomes. Elevated hepcidin levels hinder placental iron transfer, limiting the supply of iron from mother to fetus. This restriction increases the risk of fetal iron deficiency, which is linked to impaired neurodevelopment and long-term cognitive deficits [24]. Additionally, maternal vitamin D deficiency and anemia have been associated with adverse pregnancy outcomes, including lower birth weight and higher rates of preterm birth [36]. These findings underscore the critical importance of addressing vitamin D deficiency and hepcidin dysregulation to safeguard both maternal and fetal health.

Diagnostic Role of Hepcidin in Vitamin D Deficiency and Iron Deficiency Anemia

Hepcidin has emerged as a biomarker of significant clinical relevance in the diagnosis and management of anemia, particularly during pregnancy. Beyond its traditional role as a regulator of iron homeostasis, hepcidin also provides diagnostic insights into the underlying interplay between vitamin D deficiency and iron deficiency anemia (IDA). This section focuses on the unique diagnostic applications of hepcidin in these contexts, emphasizing its role in identifying and stratifying anemia types, predicting treatment responses, and guiding precision medicine in high-risk pregnancies.

Hepcidin as a Biomarker of Iron Metabolism

Hepcidin plays a central role in regulating systemic iron levels, serving as a dynamic biomarker that reflects real-time physiological responses to fluctuations in iron status, inflammation, and erythropoietic activity. Unlike static markers such as ferritin or serum iron, hepcidin levels adjust to environmental and pathological conditions, providing critical insights into iron metabolism [37].

In cases of functional iron deficiency, elevated hepcidin levels signal iron sequestration within macrophages and reduced intestinal iron absorption, key characteristics of anemia of inflammation (AI). This is in contrast to iron deficiency anemia (IDA), where low hepcidin levels correspond to systemic iron depletion [38]. Additionally, hepcidin measurements offer predictive value in determining the effectiveness of iron supplementation. By assessing whether elevated hepcidin is actively blocking dietary iron absorption, clinicians can better tailor interventions to optimize iron bioavailability and treatment outcomes [39].

Hepcidin in the Context of Vitamin D Deficiency

Vitamin D influences hepcidin expression through both direct and indirect mechanisms, as previously discussed. Beyond these mechanistic insights, the diagnostic utility of hepcidin in the context of vitamin D deficiency provides valuable clinical information.

Elevated hepcidin levels in vitamin D deficiency indicate a functional iron blockade that differs from dietary iron insufficiency. Recognizing this distinction is essential for determining whether vitamin D supplementation should be incorporated alongside iron therapy [40].

Additionally, vitamin D deficiency is often associated with heightened inflammation, which further elevates hepcidin levels. Combining hepcidin measurements with inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6) offers a more comprehensive diagnostic approach, enabling clinicians to differentiate between simple iron deficiency and inflammation-driven iron dysregulation [41].

For instance, pregnant women with low vitamin D levels and elevated hepcidin concentrations are more likely to benefit from dual therapy targeting both inflammation and iron deficiency rather than iron supplementation alone. This integrated approach can improve treatment efficacy and maternal-fetal outcomes.

Hepcidin as a Predictor of Treatment Outcomes

Hepcidin serves as a valuable predictive marker for assessing treatment responses in both iron deficiency anemia (IDA) and vitamin D deficiency. Its utility lies in guiding therapeutic decisions and monitoring treatment efficacy.

Serum hepcidin levels are instrumental in determining the likelihood of success with oral iron supplementation. Elevated hepcidin levels predict poor absorption and limited efficacy of oral iron, suggesting that intravenous iron therapy may be a more suitable intervention. This has been supported by studies demonstrating that pregnant women with elevated hepcidin levels experienced significant benefits from intravenous iron formulations compared to oral iron [42].

Additionally, hepcidin is a useful marker for evaluating the effects of vitamin D supplementation. A reduction in hepcidin levels following vitamin D therapy indicates effective suppression of inflammation-driven iron sequestration, providing an early indicator of therapeutic success in managing concurrent vitamin D deficiency and IDA [43]. These applications underscore the importance of incorporating hepcidin measurements into personalized treatment strategies for optimizing patient outcomes.

Combining Hepcidin with Other Biomarkers

While hepcidin offers valuable diagnostic insights on its own, its clinical utility is significantly enhanced when combined with other biomarkers, providing a more comprehensive understanding of iron metabolism and anemia etiology.

Ferritin and transferrin saturation are traditional markers of iron status, but their interpretation can be complicated in certain contexts. Ferritin reflects total iron stores but may be falsely elevated in inflammatory states. In such cases, hepcidin measurements can help determine whether high ferritin levels indicate true iron sufficiency or functional sequestration [44]. Similarly, combining hepcidin with transferrin saturation aids in distinguishing between iron deficiency anemia (IDA) and anemia of inflammation (AI) [45].

Incorporating vitamin D status, specifically measuring 25-hydroxyvitamin D levels, further refines the diagnostic process. This approach is particularly valuable in populations at high risk for concurrent vitamin D deficiency and anemia, allowing for a nuanced understanding of anemia's underlying causes [46].
Finally, integrating hepcidin with inflammatory markers such as interleukin-6 (IL-6) and C-reactive protein (CRP) offers insights into the inflammatory drivers of anemia. This combination not only facilitates more accurate diagnosis but also highlights the potential benefits of anti-inflammatory interventions, including vitamin D supplementation, for managing anemia in inflammatory contexts [41].

Hepcidin's Role in High-Risk Populations

Certain populations are particularly affected by the interplay between vitamin D deficiency and iron deficiency anemia (IDA), highlighting the diagnostic value of hepcidin in these groups.
Obese pregnant women often experience chronic low-grade inflammation, which drives elevated hepcidin levels. In such cases, measuring hepcidin can identify individuals who are unlikely to benefit from oral iron therapy alone, guiding the use of alternative treatments such as intravenous iron [34]. Similarly, women with gestational diabetes mellitus (GDM) face exacerbated systemic inflammation, leading to higher hepcidin levels and reduced iron bioavailability. Hepcidin-guided diagnostics can help differentiate anemia caused by GDM-associated inflammation from anemia due to dietary iron deficiency, allowing for more tailored therapeutic approaches [23].
In low-resource settings, where access to advanced diagnostic tools is limited, point-of-care hepcidin assays offer a practical and cost-effective solution. These assays enable rapid screening for functional iron deficiency, providing crucial guidance for targeted interventions in populations with high anemia prevalence [47]. This adaptability makes hepcidin an invaluable tool for improving anemia management in diverse and underserved populations.

Emerging Diagnostic Technologies

Recent advances in diagnostic technologies are enhancing the feasibility of integrating hepcidin measurements into routine clinical practice, providing more precise tools for evaluating iron metabolism.
Liquid chromatography-tandem mass spectrometry (LC-MS/MS) remains the gold standard for measuring hepcidin due to its exceptional sensitivity and specificity. However, the high cost and technical complexity of this method currently limit its widespread clinical application. To address this gap, enzyme-linked immunosorbent assays (ELISA) have emerged as a more accessible alternative. Commercially available ELISA kits provide reliable hepcidin measurements, making them suitable for clinical use and increasingly popular in both research and practice [48].
Further innovation is focused on point-of-care testing, with efforts underway to develop rapid and portable hepcidin assays. These tests have the potential to be particularly valuable in antenatal care clinics and low-resource settings, where traditional diagnostic infrastructure is limited [49]. Such advancements hold significant promise for expanding the clinical utility of hepcidin, enabling broader access to its diagnostic and predictive benefits.

Therapeutic Implications: Vitamin D and Hepcidin as Targets

The intricate interplay between vitamin D and hepcidin offers unique opportunities for targeted therapeutic strategies to manage iron deficiency anemia (IDA) during pregnancy. While traditional approaches focus primarily on iron supplementation, incorporating interventions that address vitamin D deficiency and modulate hepcidin levels provides a more comprehensive solution. This section explores the therapeutic potential of targeting both vitamin D and hepcidin, emphasizing innovative treatments and integrated approaches that avoid redundancy with earlier sections.

Addressing Vitamin D Deficiency to Modulate Hepcidin

Vitamin D supplementation serves a dual purpose in managing iron deficiency anemia (IDA) by directly suppressing hepcidin expression and mitigating inflammation-driven anemia. Emerging evidence highlights several therapeutic benefits of vitamin D in this context.

High-dose vitamin D therapy, such as weekly doses of 50,000 IU, has been shown to significantly reduce serum hepcidin levels within weeks. This reduction enhances iron absorption and mobilization, particularly benefiting pregnant women who experience concurrent vitamin D deficiency and inflammation-driven anemia [43]. Additionally, vitamin D's anti-inflammatory properties, specifically its ability to reduce pro-inflammatory cytokines like interleukin-6 (IL-6), indirectly lower hepcidin levels and improve iron bioavailability [50]. This mechanism is especially critical for populations with chronic inflammation, such as individuals with obesity or gestational diabetes mellitus (GDM).

Moreover, vitamin D supplementation acts as an effective adjunct to iron therapy. By modulating hepcidin levels, vitamin D enhances the efficacy of iron supplementation, reducing the likelihood of treatment failure in patients with elevated hepcidin [6,51]. However, optimal dosing strategies for vitamin D supplementation during pregnancy remain an area of ongoing research. Tailoring vitamin D doses based on individual baseline levels and hepcidin concentrations may further improve therapeutic outcomes and maternal-fetal health.

Hepcidin-Targeted Therapies

Hepcidin has emerged as a promising therapeutic target for managing refractory anemia, particularly in cases where elevated hepcidin levels impede iron absorption and mobilization. Innovative treatments targeting hepcidin and its downstream effects offer new avenues for improving iron homeostasis and anemia management.

Hepcidin antagonists, including monoclonal antibodies and small interfering RNAs (siRNAs) that inhibit hepcidin or its receptors, are currently under development. These therapies directly neutralize hepcidin activity, thereby bypassing its inhibitory effects on ferroportin, the iron-exporting protein. Early clinical trials have demonstrated encouraging results in enhancing iron availability in chronic inflammatory conditions, with potential applications for pregnancy-associated anemia [52].

Ferroportin stabilizers represent another innovative approach. These drugs are designed to maintain ferroportin functionality even in the presence of elevated hepcidin levels, ensuring the continued export of iron from enterocytes and macrophages [11]. This strategy aims to sustain adequate iron supply despite the hepcidin-induced blockade.

The combination of hepcidin-targeted therapies with anti-inflammatory agents further enhances their efficacy, especially in conditions where inflammation contributes to anemia. Examples include preeclampsia or obesity-related anemia, where dual interventions could simultaneously address the inflammatory and iron-regulatory aspects of the condition [53]. These emerging therapies offer hope for more effective management of complex anemia cases.

Combined Therapeutic Strategies

Addressing the dual burden of vitamin D deficiency and elevated hepcidin requires integrated therapeutic strategies that simultaneously target both pathways, optimizing anemia management and improving patient outcomes.

A combination of vitamin D and iron supplementation has shown synergistic benefits in clinical trials. High-dose vitamin D reduces hepcidin levels, enhancing iron absorption, while iron supplementation replenishes systemic and stored iron reserves [54]. This dual approach is particularly effective in cases where both deficiencies coexist. In more severe cases of refractory anemia or when hepcidin levels are significantly elevated, intravenous iron offers a direct solution by bypassing the gastrointestinal absorption blockade.

When paired with vitamin D supplementation, this strategy not only corrects iron deficits but also sustains hepcidin suppression and reduces inflammation [55].

Personalized interventions based on biomarker-guided therapy provide an additional layer of precision. Measuring serum hepcidin, ferritin, and vitamin D levels allows clinicians to tailor treatment plans to individual needs. For instance, women presenting with high hepcidin levels and low vitamin D concentrations are likely to benefit most from combined vitamin D and intravenous iron therapy [56].

Public Health and Future Perspectives

The global burden of vitamin D deficiency and iron deficiency anemia (IDA) during pregnancy poses significant challenges to maternal and neonatal health. These interconnected conditions necessitate a multifaceted approach encompassing public health strategies and cutting-edge research to improve outcomes.

Public Health Recommendations

Routine Screening for Vitamin D and Hepcidin Levels

Incorporating biomarkers such as serum 25-hydroxyvitamin D and hepcidin into antenatal screening programs can enhance early identification of at-risk populations. Screening tools need to be accessible, particularly in low-resource settings, and should prioritize high-risk groups such as women with obesity, gestational diabetes mellitus (GDM), or inflammatory conditions [57]. Hepcidin, a dynamic biomarker of iron regulation, helps differentiate between anemia of inflammation and absolute iron deficiency, thereby guiding tailored interventions.

Nutritional Supplementation and Fortification Programs

Public health campaigns promoting combined vitamin D and iron supplementation have demonstrated improved treatment efficacy by enhancing iron absorption and mitigating inflammation-driven anemia. The fortification of staple foods with iron and vitamin D has shown promise in addressing population-wide deficiencies. Studies suggest that fortified breakfast cereals and vitamin D-enhanced juices can improve iron bioavailability and reduce the risk of IDA during pregnancy [58].

Future Research Directions

Despite advances in understanding the interplay between vitamin D, hepcidin, and IDA, several gaps remain. Addressing these gaps is critical for optimizing maternal and neonatal health outcomes. Further research should investigate the molecular mechanisms linking vitamin D deficiency, hepcidin, and iron metabolism. Specifically, studies are needed to clarify how vitamin D modulates hepcidin suppression during inflammation and how this interaction affects erythropoiesis [59]. Longitudinal studies are also essential to track changes in vitamin D, hepcidin, and iron parameters throughout pregnancy and postpartum. Understanding these dynamics will help refine the timing and dosage of interventions to maximize their impact.

Emerging therapies targeting the hepcidin and vitamin D pathways offer promising advancements in the management of refractory anemia, particularly in cases where conventional treatments are insufficient. Hepcidin antagonists, including monoclonal antibodies and small interfering RNAs (siRNAs), are being developed to suppress hepcidin activity directly. These innovative therapies show significant potential in clinical trials, offering a targeted approach to overcome hepcidin-mediated iron sequestration and improve iron bioavailability [52].

Additionally, advanced drug delivery systems are being explored to optimize the efficacy of vitamin D and iron supplementation. Nanoparticle-based formulations are a notable example, designed to enhance the bioavailability of these therapies while minimizing associated side effects [60]. Such innovations could

revolutionize treatment paradigms, providing more effective and tolerable options for patients with refractory anemia.

Conclusions

Vitamin D deficiency and iron deficiency anemia (IDA) are prevalent and often coexisting conditions during pregnancy, with profound implications for maternal and fetal health. The suppression of hepcidin by vitamin D is a pivotal mechanism that enhances iron absorption and mobilization, underscoring the importance of addressing both conditions concurrently.

Emerging evidence supports the integration of hepcidin as a diagnostic biomarker alongside vitamin D status to differentiate between anemia types and guide personalized treatments. Combined supplementation strategies targeting vitamin D and iron have shown synergistic benefits, improving hemoglobin levels and overall iron bioavailability. Additionally, novel hepcidin-targeted therapies hold promise for managing refractory anemia, especially in cases involving inflammation-driven iron dysregulation.

From a public health perspective, early screening for vitamin D and hepcidin levels, combined with cost-effective nutritional interventions, can significantly reduce the burden of anemia during pregnancy. Tailored approaches for high-risk populations and the development of affordable diagnostic tools are critical for addressing disparities in maternal health outcomes globally.

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