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Research Article

Metabolism of hepcidin and iron in pregnant women: pathophysiology and research results

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Abstract

Pregnancy is characterized by changes in iron metabolism due to the needs of the growing fetus, placenta and increased circulating blood volume. Hepcidin, the main hormone regulating systemic iron metabolism, plays a key role in maintaining the balance between iron intake, storage and transport. This pathophysiological review reviews the current understanding of hepcidin regulation during pregnancy, including our own studies. The study included 33 pregnant women in whom hemoglobin, serum iron and hepcidin levels were determined. Descriptive statistics, correlation and regression analyses were used for the analysis ($p < 0.05$ was considered significant). A statistically significant positive association was found between hemoglobin and hepcidin levels: Hepc = –23. 87 + 0. 25 × Hb ($r = 0.62$; $p = 0.0003$). A moderate inverse correlation was also observed between hepcidin levels and serum iron levels: Hepc = 0.0569 + 0.309 × Fe ($r = -0.66$; $p < 0.001$). These results confirm that hepcidin levels increase with increasing hemoglobin levels, reflecting its inhibitory effect on iron absorption. High hepcidin levels may reduce circulating iron levels associated with inflammation. These data demonstrate the value of hepcidin in assessing iron metabolism disorders during pregnancy and allow it to be considered as a potential biomarker for determining the type of anemia.

Keywords: hepcidin, pregnancy, hemoglobin, iron metabolism, pathophysiology

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1. Introduction

Pregnancy is a physiological condition accompanied by significant changes in the hematopoiesis and metabolism system, including iron metabolism. The need for iron in a pregnant woman increases threefold compared to a non-pregnant woman and averages about 1000-1200 mg over the entire gestation period [1]. This is because the growing fetus and placenta, as well as the mother's blood volume, depend on iron. At the same time, iron deficiency in pregnant women is associated with a high risk of iron deficiency anemia (IDA), premature birth, low newborn body weight and increased perinatal mortality [2]. Up to 75% of all occurrences of anemia in pregnant women are caused by IDA, making it the most prevalent kind of anemia during pregnancy [3]. However, along with it, anemia of chronic diseases is often found due to inflammatory activation, in which the availability of iron for erythropoiesis is limited, despite its presence in the depot. Because it controls iron absorption in the intestine and its mobilization from macrophages and liver depots, the liver peptide hormone hepcidin is an essential regulator of iron metabolism in this respect [4]. Hepcidin acts through binding to the transmembrane protein ferroportin, which leads to its degradation and, consequently, blocks the release of iron into the systemic bloodstream [5]. A decrease in hepcidin levels increases iron absorption, while an increase in iron, especially in inflammatory conditions, leads to functional iron deficiency, despite normal or increased reserves. During pregnancy, hepcidin levels decrease physiologically, especially in the second and third trimesters, which ensures an adequate supply of iron to the fetus [6]. However, the mechanisms of hepcidin regulation in this period have not been fully studied. This work is aimed at reviewing existing data on hepsin and presenting the results of our own research demonstrating its relationship with hemoglobin and serum iron levels in pregnant women.

2. Materials and methods

2.1. Research design

The clinical study was conducted using a single-stage cross-sectional design. A total of 33 pregnant women were examined and the relationship between hepcidin, hemoglobin and iron levels were studied. All pregnant women were in the perinatal center and the Obstetrics and Gynecology Department of the Aktobe Medical Center (AMC), Aktobe, Kazakhstan. The study was carried out in compliance with the Declaration of Helsinki's ethical guidelines at the request of the West Kazakhstan Marat Ospanov Medical University's local Bioethics Committee (protocol No. 5 dated March 13, 2020). Laboratory parameters were determined in the IN VITRO laboratory in Aktobe.

2.2. Statistical Analysis

The results were analyzed by methods of descriptive, correlation, and nonparametric statistics using the Mann-Whitney test to determine differences in value for small groups, and linear regression analysis for interactions between the main parameters. The difference was considered statistically significant at P>0.05.

3. Results

Analysis of the relationship between the hemoglobin level and hepcidin concentration in pregnant women revealed a tendency toward a direct moderate correlation. According to the linear regression equation Hepc = –23.87 + 0.25 × Hb (r = 0.62; p = 0.0003) **(Figure 1),** as the hemoglobin level increases, so does the hepcidin level. This corresponds to the physiological mechanism: with sufficient iron intake, hepcidin suppresses its absorption in the intestine and release from the depot. The pathophysiological significance of a low hepcidin level with a decrease in Hb may indicate iron deficiency anemia, and elevated hepcidin with low hemoglobin is a possible sign of anemia of chronic diseases or an inflammatory process in which hepcidin increases regardless of iron stores. Thus, the hepcidin level may play a role as an additional parameter for clarifying the cause of anemia in pregnant women, especially with normal or borderline ferritin and hemoglobin values.

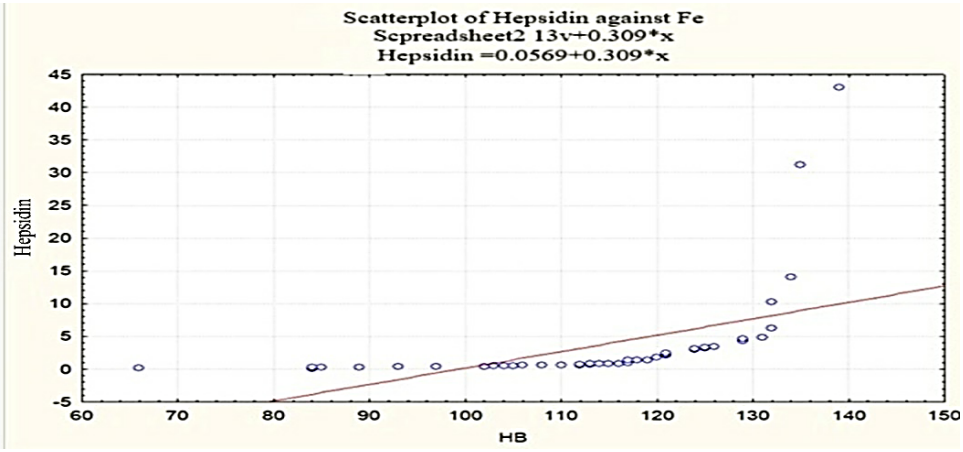

Figure 1: Correlation between hepcidin and hemoglobin levels.

Scatter plot illustrating the relationship between serum iron (Fe, μmol/L) and hepcidin concentration (ng/mL) in pregnant women. Each point represents a single case. The red line shows the linear regression trend (Hepcidin = 0.0569 + 0.309 × Fe), (r = 0.66; p < 0.001) indicating a weak inverse relationship between serum iron and hepcidin levels **(Figure 2).**

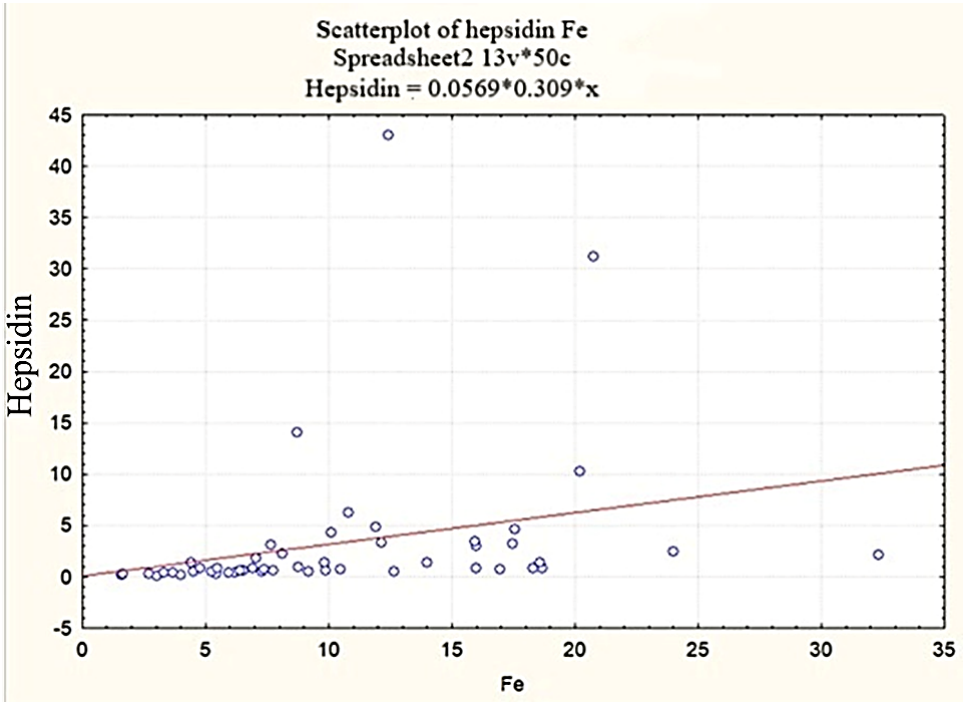

Figure 2: Correlation between hepcidin and serum iron. (https://doi: 10.23750/abm.v94i1.12713).

The data obtained indicate that there is a weak direct relationship between serum iron levels and hepcidin concentrations in pregnant women. The positive slope of the regression line (0.309) confirms the physiological mechanism of regulation: an increase in iron levels stimulates the synthesis of hepcidin, aimed at limiting further intake and mobilization of iron from the depot. However, the variation in values, especially at normal and elevated Fe concentrations, indicates a significant influence of other factors, possibly inflammation (for example, IL-6), anemia, or metabolic changes characteristic of pregnancy. The presence of high hepcidin values in some patients with moderate iron levels may indicate chronic inflammation or impaired iron transport. Thus, despite the trend, it cannot be assumed that the level of hepcidin depends on serum iron in a strictly linear manner. This highlights the need for a study including other indicators of iron metabolism (ferritin, transferrin, sTfR) and inflammation (CRP, IL-6) to more accurately assess the pathophysiological status of pregnant women with anemia.

4. Discussion

The results of this study confirm the key role of hepcidin in the regulation of iron metabolism in pregnant women. A moderate positive correlation found between hepcidin and hemoglobin ($r = 0.62$; $p = 0.0003$) indicates that hepcidin synthesis is activated by increasing hemoglobin levels. This corresponds to the physiological mechanism of negative feedback, in which the body regulates iron absorption depending on the degree of saturation [1, 7, 8]. The established negative relationship between hepcidin and serum

iron levels ($r = -0.66$; $p < 0.001$) reflects its inhibitory effect on iron mobilization from depots. High hepcidin levels cause degradation of ferroportin, a protein that ensures iron export from cells, which leads to functional iron deficiency despite normal or increased iron stores in the body [2, 8, 9]. During pregnancy, hepcidin levels physiologically decrease, particularly in the second and third trimesters, due to increased fetal iron requirements and increased maternal erythropoiesis [3, 10]. However, in the presence of inflammation such as urinary tract infection, preeclampsia or obesity, hepcidin levels may be abnormally elevated under the influence of prionflammatory cytokines such as interleukin-6 [4, 11].

Hepcidin is considered a promising biomarker of functional iron deficiency, particularly in challenging clinical situations where traditional measures such as ferritin and iron fail to differentiate between true and inflammatory iron deficiency [5, 12]. Furthermore, emerging data suggest the potential of hepcidin as a target for therapeutic intervention in inflammatory anemia and iron deficiency states [6, 13].

The results obtained in this study are consistent with the literature and highlight the importance of including hepcidin assessment in the diagnostic algorithm for anemia during pregnancy.

5. Conclusion

During the study, hepcidin showed a statistically significant relationship with the main indicators of iron metabolism during pregnancy: a positive correlation with hemoglobin levels and a negative correlation with serum iron concentrations. The level of hepcidin reflects the balance between the need and availability of iron and can fluctuate under the influence of inflammatory processes. The inclusion of hepcidin analysis in the clinical algorithm for diagnosing anemia in pregnant women may make it possible to accurately identify its causes and choose an adequate therapy.

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Conflict of Interest

Each author has no conflict of interest related to the presented article.

Ethical Statement

Ethical Committee of the West Kazakhstan Marat Ospanov Medical University has considered and approved the presented research as conducted in Ethical principles (protocol no. 5 from 13.03.2020).

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