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Ferritin and Evaluation of Maternal Serum Ferritin Concentrations as a Predictor of Preterm Labour

Abdelrazik Elsayed Abdelrazik , Mohamed A. Ibrahem, Mohamed Abdelsalam Fathy Mohamed , Ahmed Hisham Saleh Radwan

Department of Obstetrics and Gynecology, Faculty of Medicine, Zagazig University, Egypt

***Corresponding author: Mohamed Abdelsalam Fathy Mohamed**

Email: Muhammadelmasrei@gmail.com

Abstract:

Preterm labour, defined as birth before 37 completed weeks of gestation, remains a leading cause of neonatal morbidity and mortality worldwide. Multiple risk factors have been identified, including maternal infections, inflammation, and nutritional deficiencies. Among these, maternal iron status has emerged as a potential determinant. Ferritin, an intracellular protein that stores and releases iron, serves as a reliable biomarker of body iron reserves. Beyond iron metabolism, ferritin is also an acute-phase reactant, rising during systemic inflammation. Several studies have suggested that both iron deficiency (low ferritin) and inflammation-related ferritin elevation may be linked to adverse pregnancy outcomes, including preterm labour. Evaluating maternal serum ferritin concentrations during pregnancy may therefore provide predictive value for preterm birth risk. Establishing this relationship could support the development of cost-effective screening and early intervention strategies, ultimately improving maternal and neonatal outcomes.

Keywords: Ferritin, Maternal serum ferritin, Iron status, Pregnancy, Preterm labour, Inflammation, Biomarker, Prediction.

Introduction:

Ferritin, the main iron storage protein, was suggested to be an adequate alternative as a screening test being a relatively cheap and easily available blood test. Its level is known to rise in response to hypoxia or as an acute phase reactant in infections. Ferritin blood level normally drops, in correlation with the progressive depletion of iron reserves, by 32% during the first trimester, 39% in the second and up to 53% during the third trimester. This level reaches a nadir at 30-32 weeks, after which it stays constant (**1).**

Ferritin is a crucial protein involved in iron storage and metabolism in the body. Its unique structure allows it to perform effectively in regulating iron homeostasis. Ferritin is a globular protein composed of 24 subunits, which can be either heavy (H) or light (L) chains. The ratio of these chains can vary depending on the tissue and physiological conditions **(2).**

The subunits form a hollow spherical shell, creating a central cavity that can store up to 4,500 iron atoms in the form of ferric ions, complexed with hydroxide ions and phosphate. The overall diameter of ferritin is approximately 12nm, with the core diameter being about 8 nm. Inside the core, iron is stored as a mineral called ferrihydrite, which is less toxic and soluble, preventing free iron from participating in harmful reactions **(3).**

Function

Ferritin serves as the primary storage form of iron in the body, allowing for safe, controlled release of iron when needed. This is essential for preventing iron deficiency and toxicity. Ferritin can release stored iron when the body requires it, such as during erythropoiesis (red blood cell production) or in response to low systemic iron levels. This release is facilitated by changes in pH and the presence of specific proteins. Ferritin

plays a key role in maintaining iron homeostasis by balancing iron storage and mobilization, thus preventing both iron deficiency and overload **(4).**

Beyond iron storage, ferritin is involved in various cellular processes. By sequestering free iron, ferritin helps prevent the formation of reactive oxygen species (ROS), which can damage cells. Ferritin may participate in cellular signaling pathways, influencing processes such as inflammation and cell proliferation. Serum ferritin levels are commonly used as a biomarker to assess iron stores in the body. Abnormal ferritin levels are associated with various conditions, including anemia, hemochromatosis, liver disease, and inflammatory disorders **(2).**

Metabolism of Iron Stores

Iron is an essential element for the living body. The human body stores iron in the form of ferritin and hemosiderin in liver, spleen, marrow, duodenum, skeletal muscle and other anatomic areas. Hemosiderin has been known as yellow-brownish granules that can be stained by Prussian blue in the tissue cells. On the other hand, ferritin is invisible by photo microscopy or may be faintly visible and stained diffusely in the tissue cells by Prussian blue, if concentrated **(5).**

Hemosiderin and ferritin are iron-containing proteins with magnetic susceptibility. Hemosiderin is water-insoluble and thermally denatured, but ferritin is water-soluble and heat-resistant up to 75°C. These characteristic differences were used for the fractionation of ferritin and hemosiderin. The total amount of body iron stores is around 600 to1000 mg in the normal adult male and around 200 to 300 mg in the normal adult female **(6).**

The amount of ferritin iron is slightly larger than hemosiderin iron in the range from iron deficiency to normal. However, the amount of hemosiderin iron becomes larger than ferritin iron in the iron overload range. Ratio of hemosiderin iron per ferritin iron increases along with the progress of iron deposition **(5).**

The prevalence of iron deficiency anemia in the menstruating female is less than 10%. However, that of iron deficiency without anemia is around 20 to 40% in the menstruating female. The amount of storage iron in the normal female increases gradually after menopause, but it is still lower than the level of the normal male even after 20 years. The main cause of iron deficiency is increased blood loss **(7).**

Storage iron behaves as if resisting change in the iron density gradient in accordance with an iron homeostasis. The transformation of ferritin into hemosiderin might be the second-best evolutionary step to reduce iron toxicity, compensating for the human body's lack of an iron excretion function **(8).**

The increase of non-transferring-bound iron, both in whole body iron overload and in localized iron deposition, produces hazardous free radicals causing various disorders. To reduce iron toxicity, phlebotomy is performed for treating hereditary hemochromatosis and chronic hepatitis C. Also, an iron chelating agent, deferasirox, is now in use for treating anemic patients with trans fusional iron overload **(6).**

Clinical Method for Determining Iron Stores

Quantitative determination of iron stores

The total amount of iron in the blood removed by phlebotomy or that in the transfused blood for patients with transfusion-dependent anemia can be determined by using the ratio of hemoglobin iron to hemoglobin. The total amount of iron stored after intravenous iron injection of patients with iron deficiency anemia can be obtained by subtracting the iron fixed in the increased hemoglobin in red cell mass from the total amount of iron injected. The total amount of iron stores divided by the term of non-iron deficiency state after iv iron infusion until the recurrence of iron deficiency gives the storage iron a decrease rate in patients with iron deficiency anemia with constant blood loss **(9).**

Semiquantitative estimation of iron stores

The correlation between the total amount of storage iron and hemosiderin grain counts from biopsy sample has been used for the estimation of iron stores. Total iron binding capacity and transferrin receptor are helpful for the diagnosis of iron deficiency states **(10).**

Body surface monitoring methods such as dual-energy X-ray CT, super conduction quantum interference device susceptometry (SQUID), and magnetic resonance imaging (MRI) were introduced. However, other than for MRI, these methods are not adopted for clinical settings. Although MRI is useful for the estimation of localized iron deposition, it has limitations regarding the quantitative determination of total amounts of storage iron in iron overload and is especially unreliable in mild iron overload range such as serum ferritin below 1500 ng/ml **(11).**

Serum ferritin may render a value higher than the actual storage iron level in patients with various inflammations, malignancies, or hereditary hyper-ferritinemia-cataract syndrome. Therefore, appropriate examinations are needed for excluding suspected cases of overestimation. Despite its disadvantages, serum ferritin has been regarded highly for the diagnosis and treatment of patients with iron deficiency anemia and iron overload **(12).**

It has been revealed that serum ferritin concentration reflects the iron stores of the body, a rate and a formula were proposed for converting serum ferritin into iron stores. However, such conversion methods do not always reflect the amount of iron stores because serum ferritin cannot reflect hemosiderin iron. The ratio of serum ferritin to iron stores was lower in the level below 1 g than that above 1 g. This may indicate the iron insufficiency for ferritin synthesis in patients with decreased but within the normal level of storage iron **(13).**

Table 1. Classifications of iron status according to storage iron levels (9).

Iron deficiency ±symptom		<decrease	Normal	increase<	Iron overload ±symptom
Iron stores	g	<0.1		2.5~5.0<	
Serum ferritin	ng/ml	<12		250~500<	
TIBC*	μg/dl	>360		~200>	

TIBC* Total iron-binding capacity of serum.

Determination of ferritin iron by serum ferritin kinetics

It has been developed a clinical method for the simultaneous determination of ferritin and hemosiderin iron by using a serum ferritin decrease curve measured in the course of iron removal therapy. The method is based on the fact that the serum ferritin decrease curve is composed of the sum of two components, one decreasing and the other recovering **(14).**

The decreasing component reflects the decrease of pre-existing tissue ferritin iron, and the recovering component reflects the increase of tissue ferritin iron by removing iron from hemosiderin. The best fit decrease curve of serial serum ferritin assay dots was selected by computer simulation with a spreadsheet program. By the above-described processing, the amount of ferritin iron and hemosiderin iron among total iron stores was determined **(15).**

In addition, a method of proportional allotment was applied for displaying the increasing and decreasing phases of ferritin iron and hemosiderin iron, and also for determining the change in proportion between pre-existing old ferritin and new ferritin synthesized by removing iron from hemosiderin in the course of iron removal. The proportion of old and new ferritin iron in the mixture of both were calculated by the formula: percent new ferritin iron = 100 × new ferritin iron/total (new + old) ferritin iron **(16).**

Increase of Iron Stores

Iron overload

Long-term positive iron-balance (absorption > loss) leads to iron overload. Iron contained in decreased hemoglobin in anemia, except for iron deficiency anemia, is added to storage. However, if storage iron is less than 1 g before the development of anemia, the total amount of storage iron after its development will stay within the normal range. The incidence of iron overload is higher in males than in females with menstrual blood loss. Generally, iron overload symptoms appear in patients with serum ferritin levels above 1000 ng/mlm **(17).**

The main causes of iron overload are blood transfusion, alcohol consumption, mistreatment and uncontrolled increase of iron absorption in patients with hereditary hemochromatosis. However, iron absorption is not always increased in iron overloaded hereditary hemochromatosis. It has been demonstrated that an increase of iron absorption in patients with hereditary hemochromatosis whose storage iron level was kept within the normal range after phlebotomy therapy **(18).**

Uncontrolled increase of iron absorption due to gene mutation results in iron overload in patients with the C282Y mutated hemochromatosis (HFE1), hemojuvelin (HJV) mutated hemochromatosis (HFE2), hepcidin antimicrobial peptide (HAMP) mutated juvenile hemochromatosis, transferrin receptor 2 (TfR2) mutated hemochromatosis (HFE3), solute carrier family 40 member 1 (SLC40A1) mutated ferroportin disease (HFE4), thalassemia major, aceruloplasminemia, congenital a trans ferrinemia and solute carrier family 11 member 2 (SLC11A2) mutated divalent metal transporter 1 (DMT1)-associated hypochromic anemia **(19).**

DMT1 is a duodenal apical iron transporter regulated by body iron stores. It is known as natural resistance-associated macrophage protein 2 (NRAMP 2). Iron removal therapy is effective not only for hereditary hemochromatosis, trans-fusional iron overload and chronic hepatitis C, but also for nonalcoholic steatohepatitis and type 2 diabetes **(20).**

Iron stores in erythrocyte precursors

Transferrin-bound iron (TfBI) binds transferrin receptor 1 (TfR1) on the surface of erythrocyte precursors. Then, the TfBI-TfR1 complex is internalized, iron is released and utilized for hemoglobin synthesis or stored. TfR1 expression and intracellular iron concentration are inversely correlated **(21).**

It has been observed that erythroblasts are surrounded by ferritin by electron microscopy. They speculated that such ferritin was supplied from "nursing cells" (marrow macrophages) to erythroblasts for hemoglobin synthesis. However, it seemed difficult to confirm the direction of ferritin movement from marrow macrophages to erythroblasts morphologically. Iron stores in red cell precursors are not an index of the body storage iron level but are affected by the serum iron level **(22).**

Sideroblasts appear in iron overload or in anemia along with disorders of hemoglobin synthesis, with excessive accumulation of iron in mitochondria. Refractory anemia with ring sideroblasts is characteristic of bone marrow erythrodysplasia and ring sideroblasts **(23).**

Iron stores and iron absorption

Food iron is absorbed through the intestine mostly via duodenum mediated by DMT1. Iron absorption is 1 mg/day in normal males and 1.2 mg/day in normal females. Iron overload is mostly caused by the increase of iron absorption **(20).**

It has been proposed that the mucosal block theory implied an automatic control of iron absorption by the saturation of ferritin formation in the mucosal epithelial cells following oral iron administration. It has been revealed that hemosiderin formation was not saturated, although ferritin formation was saturated in rats after oral iron administration. He then thought that incomplete blockage of iron absorption could occur by way of hemosiderin formation in the enterocytes **(24).**

Iron can enter the duodenal epithelial cells from both blood circulation and intestine. The total body storage iron level is reflected in the storage iron level in enterocytes. Iron entering the enterocytes via intestine

becomes intracellular labile iron temporarily and is synthesized into ferritin and hemosiderin in the enterocytes. Thus, stored iron in the enterocytes becomes intracellular labile iron temporarily and enters blood circulation (absorbed) sooner or later in negative iron balance, or it is lost by exfoliation **(25).**

Iron absorption is inversely correlated to the amount of iron stores. However, iron absorption normalizes before the storage iron level normalizes, along with the recovery of hemoglobin in the course of treatment of iron deficiency anemia. It has been revealed that the larger the iron stores before iron removal, the faster the rebound by acceleration of iron absorption after phlebotomy therapy for patients with chronic hepatitis C. Such a trend of rebound is also observed in hereditary hemochromatosis after phlebotomy therapy **(26).**

The increase of hemosiderin per ferritin ratio in hereditary hemochromatosis is not as marked as that of chronic hepatitis C. The relative increase of hemosiderin iron in hepatocytes of chronic hepatitis C with a normal level of iron stores suggests the difficulty of storing iron in the form of ferritin in the hepatocytes suffering from chronic hepatitis C **(17).**

A mild anemia observed in iron-overloaded patients with hereditary hemochromatosis disappears after phlebotomy therapy. Similarly, anemia in transfusion-dependent patients is improved after iron removal by deferasirox. Thus, iron absorption, erythropoietic activity, hepcidin and storage iron interact as the main regulators of iron homeostasis **(27).**

On the other hand, the mechanism of uncontrolled increase of iron absorption in patients with gene mutations cannot be explained simply by the action of hepcidin. Low hepcidin in hereditary hemochromatosis indicates the derangement of the sensing system to the storage iron level due to hemochromatosis (HFE) gene mutations. The mechanisms of uncontrolled iron absorption in gene mutated patients are investigated extensively in relation with iron sensing proteins of HJV, transferrin receptor 2, HFE, iron regulatory protein (IRP) and others, but much remains to be elucidated **(28).**

Iron entering the body via parenteral routes

Iron entering the body through parenteral routes follows different courses from the iron absorbed via the enteric route. The transfused senescent red cell or intravenously injected colloidal iron is captured by the reticuloendothelial (RE) phagocytes. There, red cell or colloidal iron is decomposed and stored temporarily. Then, the stored iron in RE is released and redistributed by transferrin to whole body tissues in proportion to the ratio of distribution of pre-existing iron. Most of the iron enters the body via respiratory tract deposits in pulmonary tissue **(29).**

Generally, hemosiderin iron per ferritin ratio increases along with the increase of iron deposition. However, after the restoration of the normal level of hemoglobin and iron stores by intravenous colloidal iron therapy to iron deficiency anemia, an increase of hemosiderin iron was higher than ferritin iron due to the increased iron concentration in RE phagocytes **(30).**

Decrease of Iron Stores

Iron deficiency

Long-term negative iron-balance (absorption<loss) results in iron deficiency. Iron deficiency implies the state of storage iron exhaustion. It can be classified into 3 stages: iron deficiency without anemia, iron deficiency anemia without tissue damage, and iron deficiency anemia with tissue damage. Iron deficiency tissue damage, so-called Paterson-Kelly or Plummer-Vinson syndrome, occurs mostly in middle-aged female patients with chronic iron deficiency anemia. Iron deficiency in the developing brain in the early stage of life seems to be a risk factor **(31).**

Iron deficiency limits hemoglobin synthesis and this knowledge is applied for the treatment of polycythemia vera. It has been revealed that iron deficiency sedated chronic hepatitis C. Furthermore, it has been observed that iron deficiency inhibited the incidence of hepatoma in chronic hepatitis C, and It has been found the inhibition of hyperthyroidism by iron deficiency **(32).**

Helicobacter pylori can survive in strong acidic circumstance by producing alkaline substance and receiving nutrient iron from lactoferrin. It has been suggested that helicobacter pylori infection triggered auto-immuune gastritis resulting in iron deficiency. Helicobacter pylori infection seems to be related to iron deficiency by decreasing iron absorption and by increasing iron loss **(33).**

Storage iron and hypoferremia

Hypoferremia is seen not only in iron deficiency anemia, but also in non-iron deficiency states with the normal level of iron stores and iron overload. The human body reserves iron probably because the supply of a sufficient amount of iron is difficult by iron absorption alone when there is an urgent need for erythropoiesis as in the case of a large amount of blood loss **(34).**

It is also difficult to mobilize storage iron fast enough to meet the acute need for iron, as in the case with erythropoiesis elevated up to 6 to 8 times the normal even when having a sufficient amount of iron reserve. The shortage of iron supply from storage at the time of an acute increase of erythropoiesis results in hypoferremia, by which the erythropoiesis is suppressed. Suppressed erythropoiesis by hypoferremia was called "iron-restricted erythropoiesis" **(35).**

Hypoferremia occurs immediately after the supplementation of essential elements, such as vitamin B12, folate, erythropoietin. in patients with element-deficiency anemia, even if patients have a sufficient amount of storage iron for recovering their previous normal hemoglobin level **(36).**

Hypoferremia occurs in inflammation anemia, a representative of anemia of chronic disease with iron-restricted erythropoiesis. Chronic kidney disease is also regarded as an anemia of chronic disease affected by interleukin-6. Hypoferremia in inflammation anemia is caused by the suppression of iron efflux from iron storing cells into plasma due to the down regulation of ferroportin by hepcidin inducing internalization and degradation of hepcidin-ferroportin complex **(12).**

It has been suggested the existence of erythropoiesis suppressing factors other than hepcidin in anemia of chronic disease. It has been reported that the hepcidin expression in anemia of chronic disease was regulated by growth differentiation factor 15. These studies disclosed the multilayered regulation of iron metabolism in anemia of chronic disease **(37).**

Hypoferremia due to inflammation can be differentiated from iron deficiency anemia by assaying serum ferritin, total iron-binding capacity, C-reactive protein and other indices, as well as by clinical manifestations. Detection of iron deficiency anemia co-existing with inflammation anemia is possible if serum ferritin is decreased below12 ng/ml. Iron administration to inflammation anemia is a contraindication; even if iron supply elevates serum iron and reticulocyte counts only temporarily, it is fraught with danger and may result in iatrogenic iron overload **(38).**

Iron loss

The amount of iron loss is around 1 mg/day, around 3% of the total plasma iron turnover rate in a normal male, and 1.2 mg/day in a normal female It is balanced with the amount of iron absorption in normal subjects. Most iron deficiencies are caused by increased blood loss. Iron is lost daily by intestinal hemorrhage and exfoliation of enterocytes in normal subjects **(39).**

Iron loss in sweat is not a significant amount, but it may be overestimated by external iron contamination. Storage iron level in the enterocytes is proportional to the total storage iron level in iron equilibrium. Therefore, the amount of iron loss by the exfoliation of enterocytes is increased in iron overload, and that is decreased negligibly in iron deficiency state. Iron is also lost by menstruation, ulcer, trauma, hemodialysis, operation and intravascular hemolysis. In intravascular hemolysis, haptoglobin-bound hemoglobin and hemopexin-bound heme are rapidly cleared from circulation, stored and reutilized, or lost by hemoglobinuria and hemosiderinuria **(40).**

Turnover of Iron Stores

Intracellular iron turnover

Iron is not only needed for ferritin synthesis, but also iron accelerates its synthesis, which results from selective translational activation by iron responsive element (IRE), and iron removal from ferritin protein shell results in the degradation of ferritin. It has been shown that DMT1 is a key mediator of iron absorption and iron transfer from endosomes into the cytosol following the uptake of the transferrin receptor complex. Above-mentioned intracellular iron turnover is under the coordinate regulation of IRPs and IREs. IREs are thought to be associated with iron regulated amyloid precursor protein transcript in Alzheimer's disease **(41).**

High serum ferritin without the increase of body storage iron level and early onset of bilateral cataract in patients with hereditary hyper-ferritinemia-cataract syndrome are caused by mutations in the IRE segment of the ferritin light chain (FTL) gene. The slower degradation of light (L)-chain ferritin than heavy (H)-chain ferritin accelerates the accumulation of ferritin in lens **(42).**

Ferritin Catabolism

Ferritin is a critical protein responsible for iron storage in the body, playing a significant role in maintaining iron homeostasis. Understanding ferritin catabolism is essential for comprehending how the body regulates iron levels and responds to various physiological conditions. Ferritin stores iron in a soluble, non-toxic form and releases it when needed, helping to prevent iron overload and deficiency. Ferritin consists of a protein shell that encapsulates iron in a mineral form, facilitating safe storage **(43).**

Ferritin can be degraded through various pathways, primarily in the liver and spleen, where iron is mobilized for use. Ferritin is often taken up by cells through receptor-mediated endocytosis. Once inside, it is transported to lysosomes. In lysosomes, ferritin is broken down by proteolytic enzymes, releasing stored iron **(1).**

The rate of ferritin catabolism is influenced by the body's iron demand. Increased demand for iron (e.g., during erythropoiesis or in response to anemia) can enhance the catabolism of ferritin to release iron. During inflammatory states, ferritin levels can increase as a response to acute phase reactions, and the rate of catabolism may be altered **(44).**

In conditions like hemochromatosis, ferritin catabolism can be impaired, leading to excess iron accumulation and toxicity. In chronic inflammatory states, ferritin levels may be elevated, but its release of iron can be decreased, contributing to functional iron deficiency. Ferritin levels are commonly used as a biomarker for iron status; understanding catabolism is crucial for interpreting these levels accurately **(45).**

Evaluation of Maternal Serum Ferritin Concentrations as a Predictor

of Preterm Labour

Preterm labour refers to labour between the onset of fetal viability and the completed 37 weeks of gestation. It represents about 10% of all births and is responsible for 75% of perinatal mortality and 50% of long-term morbidity. The pathophysiology of preterm labour is still largely unknown. However, there is evidence which indicates that subclinical infections, intrauterine infection and chronic inflammation are strong risk factors that subsequently cause preterm labour and premature rupture of membranes (PROM) **(46).**

Other risk factors include history of previous preterm labour, history of previous abortion, pregnancies conceived with assisted reproductive technologies, multifetal gestation, vaginal bleeding in pregnancy, moderate to severe anemia at 12 weeks of gestation, short cervix, cervical incompetence, previous cervical surgery, uterine problem, lifestyle factors such as low socioeconomic status, low weight gain and substance abuse during pregnancy **(47).**

In cases of infection, microorganisms produce prostaglandins either directly or via producing phospholipase A2. The action of prostaglandins is uterine contraction, and they also contribute to cervical softening **(48).**

Various biochemical markers have been developed to predict preterm labour. These markers include fetal fibronectin in the cervicovaginal secretions, human chorionic gonadotropin in the cervicovaginal secretions, maternal serum corticotropin-releasing hormone (CRH), maternal serum alpha-fetoprotein (AFP) at 11–13 weeks. This might be explained by the status of an acute phase reaction to subclinical infections that are commonly associated with preterm labour. It has been hypothesized that subclinical maternal infection is responsible for both the elevated maternal serum ferritin levels and for spontaneous preterm PROM **(46).**

Ferritin is a highly symmetrical and stable iron-containing protein that was discovered, crystallized and named in 1937, 80 years ago. It was defined as the major iron storage protein since it possesses a large cavity that can accumulate great amounts of iron. One of the ferritin major properties is its capacity to attract iron ions and to induce their mineralization by using its ferroxidase activity together with the chemical properties specific of the cavity environment **(2).**

The mineral core can contain up to 4000 Fe atoms in a mineral form and is protected and maintained in solution by the protein coat. Ferritin is almost ubiquitous, and a number of functions have been attributed to it. Its location is manly cytoplasmic; however, it has been found also in nucleus, in animal mitochondria, in plant plastids, in insect ER, and it is also secreted in the circulating plasma. Although extensively studied, the particular chemical and biological properties of the various ferritins are still attracting researchers; thereby new lines of research are developing in many different fields (**1).**

The easy production of recombinant ferritins and their genetic manipulation, joined to the efficient self-assembly, has been exploited in an increasing variety of fascinating nanomaterial applications, and in fact ferritin seems to be the most popular protein for nanotechnologists **(2).**

Ferritin as an intracellular iron storage protein has been identified as a diagnostic marker that its high serum levels are associated with a variety of acute phase reactions, including inflammatory conditions **(13).**

Ferritin is a protein that stores iron and releases it in a controlled manner. Adequate iron levels are essential during pregnancy for maternal health, fetal growth, and development. Low iron levels can lead to anemia, which is associated with adverse pregnancy outcomes, including preterm labor. Conversely, elevated ferritin levels may indicate iron overload or inflammation, both of which can also affect pregnancy outcomes **(49).**

It has been shown women with iron deficiency anemia are at higher risk for preterm birth. Low ferritin levels reflect depleted iron stores, which may compromise placental function and fetal health. It has been found that pregnant women with ferritin levels below a specified threshold had a significantly higher incidence of preterm labor compared to those with adequate ferritin levels **(50).**

Conversely, it has been suggested that elevated ferritin levels may also be linked to adverse pregnancy outcomes. High ferritin concentrations can indicate systemic inflammation, which is a recognized risk factor for preterm labor. Elevated ferritin levels during pregnancy have been associated with conditions such as gestational diabetes and preeclampsia, both of which can contribute to preterm labor **(51).**

The relationship between maternal serum ferritin and preterm labor may be influenced by several mechanisms. Sufficient iron levels are crucial for hemoglobin production, affecting oxygen delivery to the fetus. Insufficient oxygen can trigger preterm labor. Both low and high ferritin levels may trigger inflammatory pathways that can lead to uterine contractions and subsequent preterm labor **(52).**

Understanding the role of ferritin in predicting preterm labor has significant clinical implications. Routine assessment of maternal serum ferritin could be integrated into prenatal care to identify women at risk for preterm labor. Targeted interventions, such as iron supplementation or dietary modifications, could be implemented based on ferritin levels to mitigate risks associated with both iron deficiency and excess **(53).**

Maternal serum ferritin concentrations may serve as a valuable predictor of preterm labor, with both low and high levels posing risks. A nuanced understanding of ferritin's role in iron metabolism and

inflammation can inform clinical practices aimed at reducing preterm birth rates. Continued research is essential to establish standardized ferritin level guidelines and develop effective interventions for at-risk populations **(54).**

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