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**NARRATIVE REVIEW**

# Association of inflammatory mediators and molecular markers of iron metabolism in pregnancies with pregestational obesity during the development of anemia: narrative review

**Short title:** Pregestational obesity and anemia in pregnancy

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## ABSTRACT

Obesity and anemia are major problems all over the world; pregnancies often suffer from these medical conditions. Obesity is associated with an increased risk of iron deficiency associated with the activation of inflammatory markers and their influence on iron regulatory pathways. All of the pregnant obese women have a mild inflammatory response, which later leads to increased hepcidin levels, thereby influencing iron metabolism. The purpose of this review was to summarize recent findings that have reported the measuring of markers of iron metabolism and inflammatory in pregestationally obese pregnancies in the development of anemia. This review examines obesity-related activation of inflammatory mediators as a potential primary cause of iron deficiency (ID) or iron deficiency anemia (IDA) in obese pregnant women. Despite numerous studies, the effect of maternal weight on the risk of developing ID/IDA during pregnancy remains unclear. Markers of iron metabolism in the background of inflammation are being considered. Pre-pregnancy obesity is associated with an increased risk of developing ID/IDA during pregnancy and in the postpartum period for mother and child.

**Key words**

Pregnancy; iron deficiency; iron deficiency anemia; obesity; inflammation.

## Introduction

Anemia is a decrease in hemoglobin levels. According to the World Health Organization (WHO), anemia in pregnant women is when hemoglobin <110 gr/l [1]. Worldwide, 38% of pregnant women are suffering from anemia. Women of fertile age are at risk, resulting in severe morbidity and mortality [2]. Hemoglobin below <70 gr/l is determined as severe anemia in pregnant women. Iron demand changes during pregnancy, decreasing by the end of the first trimester and increasing more than triply by the third trimester due to increased placental requirement, fetal growth, increased mother's red blood cell production, and maternal iron replenishment.

Anemia during gestation can contribute to preterm birth, low birth weight, and an increased risk of anemia in younger children. The mothers with anemia also experience the typical signs of anemia: tiredness, headaches, lethargy, and decreased functioning. Severe anemia can lead to antenatal fetal mortality or infant death. In infants, iron reserves are depleted by approximately 6 months of age, and iron deficiency (ID) or iron deficiency anemia (IDA) develops when iron intake is inadequate. Subsequently, behavioral, cognitive and motor development can be impaired in the child. Despite the worldwide efforts of scientists to prevent or treat it, iron deficiency anemia continues to be a serious international problem [3, 4].

Another global epidemic affecting bazillions of people is obesity. Obesity and ID/IDA are two forms of the world's most common eating disorders. Both obesity and ID/IDA are serious diseases in their own right. Over the past fifty years, the widespread prevalence of obesity has increased. More than billions people are now considered to have a body mass index (BMI) of more than 30 kg/m2 and this number is expected to increase over the following thirty years. A diagnosis of obesity is identified as a BMI >30 kg/m2. In pregnancies, a BMI of 30 kg/m2 or higher in the first trimester is defined as obesity, a BMI of 25.0-29.9 kg/m2 is defined as overweight, and a BMI of 18.5-24.9 kg/m2 is defined as a normal index. Classification of obesity is divided into class I (BMI 30 and <35), class II (BMI 35 and <40), and class III (BMI 40 and above) [5]. Maternal obesity is associated with an increased risk of developing gestational diabetes, preeclampsia, intrauterine growth restriction, congenital anomalies, fetal malformations, stillbirth, infant death, preterm delivery, cesarean section and an increased risk of low Apgar score [ 6, 7, 8, 9]. Maternal obesity also increases the probability of childhood obesity and type 2 diabetes in mothers and their children in the future [10, 11].

This review assesses whether obesity-induced inflammation may contribute to the increased incidence of ID/IDA in pregnant women. Despite numerous studies, the effect of maternal weight on the risk of ID/IDA during pregnancy remains unclear. Iron status metabolism markers against inflammation are considered. Pre-pregnancy obesity carries a greater risk of developing ID/IDA during pregnancy and the postnatal period for the mother and the baby.

## How obesity contributes to Anemia during pregnancy?

Obesity is a low-grade chronic inflammatory disease associated with increased hepcidin expression and, secondarily, with iron homeostasis [12]. A study in Mexico showed that obese women have higher hepcidin concentrations and a twofold higher risk of iron deficiency than unobese women. Hepsidin is a key regulator of iron metabolism in the body and has been recognized as one of the connections between obesity and IDA [13]. Hepcidin is a hormone that regulates systemic iron. This hepcidin boost causes hypoferremia, defined by a rise in solvable transferrin receptor (sTfr) and a reduction in serum iron (Fe), while ferritin is also increased [14, 15]. Hepcidin is mainly produced in

the liver and controls the mobilization of iron stores in the body through post-translational regulation of Fpn-1. However, hepcidin is also produced in the heart, adipose tissue, placenta, and kidneys. However, it remains unclear whether the hepcidin produced by these peripheral tissues has a local and/or systemic effect. Several studies have examined hepcidin concentrations during pregnancy. During physiologic pregnancy, hepcidin decreases significantly from an almost undetectable level before the end of the third trimester [16, 17, 18]. Endogenous estrogen, which increases dramatically during pregnancy, probably plays a significant role in suppressing hepcidin levels [19]. Suppression of maternal hepcidin ensures active expression of Fpn-1 at major sites of iron flow, including maternal intestinal enterocytes, liver stores, and the placenta. The fetus also produces hepcidin, but the role of fetal hepcidin in regulating iron flow through the placenta remains unknown [20]. There is evidence that maternal hepcidin is overexpressed in the 3rd trimester, maternal iron is utilized with food, and the transfer of iron through the placenta is reduced [21, 22].

Particularly, enhanced inflammation and the expression of leptin stimulate hepcidin secretion in the liver. The elevated level of hepcidin in the blood binds to ferroportin (in enterocytes), causing its disruption. Consequently, the outflow of iron into the bloodstream is prevented, resulting in inflammatory anemia. Iron deficiency (DI) can arise despite high ferritin levels due to the direct action of hepcidin on ferroportin [23]. During enhanced erythropoiesis, red blood cells release the hormone erythroferrin, which diminishes hepcidin production, thereby ensuring the release of cellular iron from reserves as well as enhancing the absorption of iron from the intestines [24, 25]. Nevertheless, the influence of erythroferrin on hepcidin in inflammatory diseases or increased blood volume during pregnancy remains not completely studied. Obesity-related inflammation promotes hepcidin expression by interleukin-6 (IL-6) in the liver and also occurs in adipose tissue. In addition, increased leptin production in enlargeed adipocytes can also contribute to high hepcidin expression [26]. Although IL-6 can be produced by activated immune cells, it is also produced by adipose tissue. Researches reveal that adipose tissue produces approximately 30% of circulating IL-6. Among other more direct actions, sometimes interleukin IL-6 causes the liver to release C-reactive protein (CRP). One way in which obesity can adversely affect iron levels throughout pregnancy is through mild inflammation, a chronic condition that can lead to CRP [27]. Specifically, it can be linked to elevated levels of inflammatory cytokines, including CRP, tumor necrosis factor-α (TNFα), and IL-6. This is observed in non-pregnant women who are overweight or obese. In the alternative, poor iron levels may result from a poor diet low in bioavailable iron and, therefore, an inability to meet elevated iron requirements during pregnancy. In a study of fifteen pregnant women with obesity and fifteen pregnant women with normal BMI, hepcidin levels were greater in the second trimester in pregnant women with obesity compared with women without obesity and were positively correlated with CRP levels. These observations suggest that an increased inflammatory profile in obese pregnant women is associated with elevated hepcidin levels [28].

A detailed number and description of pro-inflammatory cytokine mediators in gestational obesity was presented in 2017 in a review by Pendeloski et al. [29]. Despite a large number of investigations, there are conflicting data on the profile of inflammatory mediators in pregnant women with obesity. Several investigations have examined the association between obesity and iron deficiency/iron deficiency anemia. Obese children are more likely to be anemic compared with their non-obese peers [13, 30].

Ferritin is an acute phase protein, and high levels of CRP and IL-6 in obese mothers are indicative of an inflammatory state. Therefore, ferritin levels may have been elevated due to an inflammatory condition. This is the total ferritin score among obese women and women with a normal body mass index. In addition, because the data came from two different studies, they differed in maternal characteristics. Flynn et al. [31] reported greatly elevated CRP and IL-6 levels in pregnant obese women compared with pregnant women with normal body mass index (BMI) without differences in serum ferritin or hepcidin levels at 15-18 weeks of pregnancy, assuming that hepcidin is not

encouraged during this period. In another study, failed to demonstrate the effect of obesity on hepcidin and iron biomarkers in pregnant women. This negative result may be explained by the fact that the participants in this study were adolescent girls, who are known to be at risk for iron deficiency regardless of obesity [32].

Cao et al. [32] evaluated the correlation between BMI before pregnancy, weight gain during pregnancy, and maternal and neonatal iron metabolism parameters (ferritin, transferrin receptor (TfR), erythropoietin (EPO), CRP, and hepcidin). In these studies included pregnant teenage women, 38% of whom were overweight or obese. The participants in this study wtre significantly younger than in the other reports, their ages ranged from 13 to 18 years old. BMI was positively associated with inflammatory markers (CRP and IL-6) and with leptin in midgestation before pregnancy, which is consistent with previous results. Only the association between BMI and leptin, however, persisted after delivery. There were no significant differences between BMI categories of pregnant women and iron status parameters (ferritin, transferrin receptor, serum iron, erythropoietin and hepcidin) in pregnancy. However, hepcidin and ferritin were significantly higher in the midpregnancy in women with grade 2 and 3 obesity (BMI 35-39.9 and 40 kg/m2, respectively) compared with thinner women. In addition, pre-gestational BMI was positively correlated with hepcidin levels in the middle of pregnancy. Inflammation does not affect iron metabolism during pregnancy, and a certain threshold of obesity-induced IL-6 levels may have to be achieved to influence hepcidin levels.

**The impact of maternal anemia on the condition of the newborn**

Also in another study of pregnant women [33], the authors reported that obese mothers had lower iron stores (ferritin) with higher hepcidin levels throughout pregnancy compared with women with a normal BMI. In this study, pregnant women without diabetes and blood samples were taken in the second and third trimesters and at the time of delivery. The research included 86 plecentas and 97 cord blood samples from 61 normal-weight, 20 overweight, and 16 obese women. Maternal ferritin correlated with transferrin receptor in all BMI groups and did not correlate with CRP, suggesting that in this cohort ferritin levels were related to iron levels rather than inflammation. From about twenty-five weeks' gestation, ferritin levels in obese women decreased and remained low until term, whereas ferritin levels in normal-weight women increased from about thirty-five weeks' gestation until term. The authors suggest that because hepcidin is highly correlated with CRP, the inflammatory pathway likely plays a role in controlling iron levels in obese pregnant women. Maternal hepcidin levels at delivery correlated strongly with cord blood hepcidin levels, but neither maternal hepcidin or cord blood hepcidin correlated with other iron parameters (serum iron, ferritin, TfR). However, other mechanisms [34, 35], such as hepcidin production by adipose tissuee, may also play a role. Excess adipose tissue not only has negative consequences for the mother, but can also adversely affect the health of the baby . In addition, this study reported that regardless of the mother's BMI, the placenta lacks iron for the placental transferrin receptor, which is critical for iron transfer to the fetus. Maternal iron status had no effect on ferritin and transferrin receptor, in the blood. The placental increase in transferrin in iron deficiency may play a key role in ensuring adequate fetal iron levels [33, 35, 36].

It was also verified that the content and distribution of adipose tissue and liver lipids in newborns depended on maternal BMI. With each unit increase in maternal BMI, there was an increase in total, abdominal, and nonabdominal adipose tissue, and an 8.6% increase in intrahepatocellular lipids. Abdominal fat tissue and infant liver lipids increased with maternal BMI within the normal range. These effects may be initial signs of metabolic abnormalities leading to adverse health throughout life [37].

**Other effects of pregestational obesity and anemia**

Maternal obesity may increase the risk of fetal macrosomia (birth weight greater than 4000 grams) [10]. This increase, in exceptional cases, becomes mainly a consequence of increased body weight. Higher fat mass at birth may contribute to obesity at a later age. This, in turn, can lead to lethargic inflammation, elevated hepcidin levels, and ultimately inflammatory anemia. There are several studies that show that umbilical cord blood ferritin levels below 76 micrograms/l are associated with significantly impaired fine motor and speech skills [35]. Two other researches agree that umbilical cord blood ferritin concentrations below 76 micrograms/l are suboptimal and are also associated with adverse effects on neurodevelopment [36]. Flynn et al. [32] reported that infants born to obese mothers had significantly reduced umbilical cord blood ferritin levels (<76 micrograms/l) compared with those born to lean mothers. However, this relationship ceased to appear when adjusting for maternal gestational age at birth, parity, method of delivery, maternal smoking status, and ethnical background. Interestingly, ethnic differences were noted: children born to black mothers had the poorest umbilical cord blood ferritin scores compared to other ethnic groups and white mothers. Analogously, a study [37] of 85 pregnant women revealed that higher maternal BMI at birth was negatively associated with umbilical cord plasma ferritin and positively associated with CRP levels. Umbilical cord hepcidin wes not correlated with maternal BMI or maternal inflammatory status. However, it was negatively related to hemoglobin and positively associated with ferritin levels. When the authors applied a BMI threshold of 35 (n = 16), markers of inflammation (CRP, IL-6, and TNF-α) in umbilical cord blood were significantly higher than in women with BMI < 35, with diabetes further contributing to the inflammatory response. These results support the body of evidence that obesity during pregnancy can cause an inflammatory response and, in turn, negatively affect the iron balance of the newborn.

Korleski et al. [8] analyzed ferritin, hepcidin, erythropoietin, reticulocytes, and CRP in 201 umbilical cord blood of newborns at high risk for ID/IDA. A total of 40% of mothers with a BMI of 30 and 37% of mothers with a BMI < 30 had gestational diabetes. Another 36% and 23% of obese and non-obese mothers, respectively, had gestational diabetes. The authors report that newborns from obese mothers had lower ferritin and hepcidin levels, whereas erythropoietin, hemoglobin, and reticulocytes were higher compared with newborns from thin mothers. Maternal BMI at delivery was positively related to neonatal erythropoietin and negatively related to hepcidin, indicating iron insufficiency in newborns. Also, a subsequent study [37] tested 180 cord blood samples from infants at high risk for iron deficiency (ferritin <50 mcg/dl, serum iron <100 micrograms/l and transferrin saturation <30%) and found that all 16 newborns with iron deficiency were born to obese mothers, 4.9 times the risk of developing iron deficiency than those with a BMI less than 30. It is worth noting that none of the participants in this research had anemia, but there were four who had low iron levels. The authors suggest that iron transportation at the placental boundary may have a negative effect in overweight/obese pregnancies, a hypothesis that requires further investigation. Similarly, Phillips et al. [39] reported that maternal obesity and excessive weight gain affect the iron status of newborns. Pre-pregnancy obesity was observed in 28.5% of women, and another 27.5% exceeded the advised weight gain during pregnancy. Umbilical cord serum ferritin levels were significantly lower and hemoglobin levels were significantly higher in children born to obese mothers. Umbilical cord serum CRP was not associated with maternal obesity. However, CRP was associated with an excess weight gain of 18 kilograms. Based on their own study, the authors conclude that obesity before pregnancy and excessive weight gain during gestation can be considered as risk factors for the development of ID in newborns. In a similar study in China [30], children born to overweight mothers had a higher incidence of ID (serum ferritin below 75 micrograms/l, directed into the bloodstream) compared with children born to normal-weight mothers. Newborn iron status (serum ferritin, body iron) was negatively related to maternal BMI before pregnancy. The sTfR levels were significantly higher and ferritin levels significantly lower in the umbilical cord blood of newborns born

to women with higher BMI. Hepcidin levels were lower in healthy, noncomplicated pregnancies compared with non-pregnant women [40].

There is abundant evidence that pre-pregnancy obesity and obese pregnancy bring an increased maternal and postpartum risk of ID/IDA, as well as negatively impacting child development [36, 37]. High levels of CRP, hepcidin, sTfR, and IL-6 have been reported in existing studies, mainly in two case studies, suggesting an inflammatory profile in pregnant obese women [30] and, thus, may play a role in the development of ID and IDA in obese women during pregnancy [37]. In addition, mothers with BMI or obesity are at greater risk of developing ID and IDA because of obstetric problems and greater frequency of obstetric interventions, which may lead to more blood loss [41, 42]. There are also studies showing that inflammation plays no role in controlling iron metabolism during pregnancy; and that children born to young obese mothers had significantly higher levels of iron and hemoglobin in their bodies compared with children of mothers with normal BMI. In the same way, differences in placental data between obese and mothers with normal BMI have been reported [43] with changes related to cellular function. Although in the third trimester of pregnancy, no differences in nutritional iron absorption have been reported between obese and normal-weight women [33].

**Prevention and treatment of anemia**

The WHO promotes daily iron supplementation during pregnancy for women who live in areas with a high prevalence of iron deficiency because the administration of prophylactic iron in women with low iron stores represents a significant benefit [1].

The iron requirement is higher in pregnant women compared to non-pregnant women. But the iron requirement decreases in the first trimester due to the interruption of menstruation and thus the daily iron requirement is about 0.8mg (2). It then increases steadily in proportion to fetal weight in the second and third trimester (the average iron content of a fetus with a body weight >3 kg is ≈270 mg) from 4 - 5 mg to 6-10 mg in the third trimester, with most of the iron accumulated during the third trimester (10, 12, 14). Iron absorption decreases in the first trimester, probably because of lower iron requirements, increases in the second trimester, and continues to increase during the remainder of pregnancy (18,20). Regardless of the exact value, it is clear that the daily iron requirement cannot be met by diet alone (45). The Centers for Disease Control and Prevention and the American College of Obstetricians and Gynecologists recommend that all pregnant patients take low-dose (27mg) iron from the beginning of pregnancy to improve maternal hematological outcomes [46, 47]. Kawata et al. showed a significant association between malnutrition and anemia and overweight/obesity in pregnant Nepalese women, indicating an urgent need for improved nutrition. In this regard, nutrition programs shall focus on the reproductive generation and families with low health literacy [48]. Thus, finding the most effective approach to predicting and managing the risks of identifying IDA throughout pregnancy is an important topic for future research.

Anemia during pregnancy leads to adverse pregnancy outcomes for both mother and fetus, including reduced physical capacity, susceptibility to infections, susceptibility to depression, premature rupture of membranes, intrauterine delayed fetal growth, fetal hypoxia, premature birth, low birth weight, antenatal fetal death, poor quality interaction with children in the postnatal period [45].

Because of the significant impact of IDA on maternal and fetal health, it is recommended that iron preparations be taken to treat iron deficiency [49]. The use of liposomal iron is well tolerated in pregnant women with IDA, showing high gastrointestinal absorption and bioavailability and low incidence of side effects [50, 51]. Another study in obese women found that, regardless of iron status, higher BMI was associated with lower iron absorption. And in infants, a higher BMI predicted worse iron status at baseline and less improvement in iron status during the intervention [52].

## Conclusions

Overall, the need for a trimesterly evaluation of iron and inflammatory status in prenatal and postpartum follow-up of pregnant women becomes apparent. Women of childbearing age who are obese tend to gain more weight during pregnancy than women with normal BMI. Because pregnant obese women are more prone to ID/IDA during pregnancy and in the postpartum period, more careful monitoring of pre-pregnancy weight and the rate of weight gain during pregnancy is necessary.

Thus, analysis of the recent scientific literature indicates that, despite numerous studies, the issue of the pathogenetic relationship between obesity and ID/IDA and early markers for their diagnosis during pregnancy remains unresolved, which undoubtedly determines the need for further research in this direction.

## Compliance with Ethical Standard

### Author's contribution:

All authors were involved in the process of writing this article: methodology, project administration, supervision, writing original draft, writing review and editing.


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Does not apply.

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### Informed consent

N/A.

### Data sharing.

Data are available under reasonable request to the corresponding author.

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