

IMPACT OF IRON DEFICIENCY AND APPROACH TO IRON ADMINISTRATION IN PREGNANCY

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Abstract- Anaemia, which is defined as a haemoglobin (Hb) concentration no lower than 10 g/dL at term, affects virtually all pregnancies, and in the majority of instances, it is induced by a physiological process rather than indicating a deficient status or underlying hematologic illness. The amount of iron in the human body is carefully controlled and is typically kept at around 40 mg/kg for women and 50 mg/kg for males. Iron balance is regulated at the levels of iron absorption by enterocytes in the duodenum and of iron mobilisation from liver parenchyma and macrophages because humans are unable to eliminate excess iron in a controlled manner. A uncommon recessive illness known as iron resistant iron deficiency anaemia (IRIDA) is characterised by hypochromic microcytic anaemia, poor transferrin saturation, and abnormally normal or high hepcidin levels. Matriptase-2, a type II serine protease, is encoded by the TMPRSS6 gene, which is the source of its mutations. There is controversy about whether or not certain individuals with a phenotype of refractory iron deficiency who have a single mutant allele of TMPRSS6 should be classified as having IRIDA. It is possible to imagine a range of situations, from the typical form of severe IRIDA caused by homozygous or compound heterozygous TMPRSS6 mutations to enhanced vulnerability to iron shortage brought on by single mutations/polymorphic alterations. Pregnancy-related physiologic anaemia is a dilutional process brought on by an increase in plasma volume. Plasma volume rises from 25% to 80% during a typical pregnancy. The increase starts at 6 weeks into the pregnancy and lasts until 24 weeks, after which there is a slower increase. The weight of the foetus is directly related to the rise in plasma volume. In women who do not take additional iron, the erythrocyte mass also rises during pregnancy, increasing by 180–250 ml, or 10%–20% more than usual. Depleted iron reserves are 49 by iron deficiency (ID). The absence of stainable reticuloendothelial iron on a bone marrow specimen is the "gold standard" for identifying ID, although in clinical practise, it is typically identified by substitute laboratory indicators as a low serum ferritin or a reduced percentage of transferrin saturation by iron. The majority of expectant individuals can take oral iron, especially when it is administered once daily or on an irregular basis. However, intravenous iron treatment is secure and efficient if the patient is refractory to oral iron or unable or unable to consume iron orally.

Key Words: Iron, pregnancy, haemoglobin, anaemia

INTRODUCTION

Anaemia, which is defined as a haemoglobin (Hb) concentration no lower than 10 g/dL at term, affects virtually all pregnancies, and in the majority of instances, it is induced by a physiological process rather than indicating a deficient status or underlying hematologic illness¹. The prevalence of severe anaemia during pregnancy, which is indicated by a Hb concentration of 11 g/dL in the first trimester or 10 g/dL in the second and third trimesters, ranges from 2% to 26% in the population under study. Anaemia is a key factor in maternal and fetal illness and mortality in less developed countries²⁻⁶. The most common pathologic cause of anaemia in pregnancy is iron deficiency anaemia (IDA), particularly in more developed countries where other anemia-producing diseases like malaria or hemoglobinopathies have less of an effect⁷⁻⁹. Anaemia is described as "low amounts of haemoglobin in the blood, as demonstrated by a lower quality or number of red blood cells"¹⁰ in order to increase oxygen delivery to the tissues. In order to categorise anaemia in pregnant women, the WHO uses the following haemoglobin cutoffs: mild anaemia is classified as 100 to 110 g/L, moderate anaemia as 70 to 100 g/L, and severe anaemia as 70 g/L.¹¹ The causes of anaemia include factors related to nutrition (such as iron and folic acid deficiencies), infectious diseases (such as malaria and helminthes), genetic conditions (such as thalassaemia), and other factors. Anaemia is characterised by a decrease in erythrocyte production, an increase in erythrocyte loss, or a combination of these factors. Pregnant women in impoverished nations are more likely to experience anaemia and its associated issues because of the combination between the physiological demands of pregnancy and the high prevalence of the aforementioned etiologies. In the world, anaemia affects 40–50% of both pregnant and non-pregnant women of reproductive age, according to the United Nations Standing Committee on Nutrition.^{12,13} Maternal haemoglobin levels are also impacted by hemodialysis during pregnancy. Adequate plasma volume expansion, which encourages uteroplacental circulation, has been associated with better pregnancy outcomes.¹⁴ Until the late second to early third trimester, when it modestly increases around week 30 as RBC mass production catches up, the haemoglobin concentration drops as plasma volume increases.¹⁵ Approximately 15 g/L less haemoglobin is expected to be lost from pre- to mid-pregnancy.¹⁶ The mother's pre-pregnancy haemoglobin levels may thus be best reflected by early pregnancy haemoglobin readings. Maternal anaemia and IUGR are related in a few scientific theories. Low amounts of haemoglobin restrict oxygen flow throughout the body, causing oxidative stress or chronic hypoxia, which may then inhibit foetal development. Another theory for iron deficiency anaemia is that it raises norepinephrine levels, which in turn trigger the synthesis of corticotropin-releasing hormone and may, in turn, restrict foetal development. IUGR has been linked to a variety of conditions

including hypoglycemia, hypocalcemia, low Apgar scores, birth asphyxia, hyperbilirubinemia, reduced immunological function, decreased mental ability, poor development, and even morbidities that persist far into adulthood. In developing countries, low birthweight is associated with 60–80% of newborn deaths, with IUGR being mostly responsible for these outcomes.^{17,18}

FERROPORTIN, AN IRON EXPORTER

The reader is directed to previous reviews¹⁹⁻²¹ for a more in-depth discussion of the management of iron balance, which is outside the purview of this review. The amount of iron in the human body is carefully controlled and is typically kept at around 40 mg/kg for women and 50 mg/kg for males. Iron balance is regulated at the levels of iron absorption by enterocytes in the duodenum and of iron mobilisation from liver parenchyma and macrophages because humans are unable to eliminate excess iron in a controlled manner. Hepcidin, a little peptide produced in the liver, controls these activities. Ferroportin, a cellular iron export protein, is internalised when hepcidin attaches to it. The reader is directed to previous reviews for a more in-depth discussion of the management of iron balance, which is outside the purview of this review. The amount of iron in the human body is carefully controlled and is typically kept at around 40 mg/kg for women and 50 mg/kg for males. Iron balance is regulated at the levels of iron absorption by enterocytes in the duodenum and of iron mobilisation from liver parenchyma and macrophages because humans are unable to eliminate excess iron in a controlled manner. Hepcidin, a little peptide produced in the liver, controls these activities. Ferroportin, a cellular iron export protein, is internalised when hepcidin attaches to it. Any source's iron absorption percentage may be increased by twofold using ID.²³ The plasma iron transport protein transferrin transports iron from the enterocyte. Under typical conditions, the quantity of iron that is both bound to transferrin and circulated is around 0.2 mg/kg.²⁴ Storage iron is found in liver parenchymal cells (5–6 mg/kg in women, 10–12 mg/kg in males) and macrophages of the spleen, bone marrow, or liver. While liver parenchymal cells absorb or release iron from or to transferrin, macrophage iron is mostly obtained via recycling of senescent erythrocytes.²⁵

Iron Refractory Iron Deficiency Anemia

A uncommon recessive illness known as iron resistant iron deficiency anaemia (IRIDA) is characterised by hypochromic microcytic anaemia, poor transferrin saturation, and abnormally normal or high hepcidin levels. Matriptase-2, a type II serine protease, is encoded by the *TMPRSS6* gene, which is the source of its mutations.²⁸ The catalytic domain is particularly vulnerable to *TMPRSS6* mutations, which can influence diverse domains of the gene.²⁷ By cleaving the cell surface BMP co-receptor hemojuvelin, this transmembrane protease, which is abundantly expressed in the liver, suppresses hepcidin transcription and reduces BMP signalling and hepcidin production.²⁹ In order to allow the compensatory mechanism of enhanced iron absorption in iron deficit, *TMPRSS6* function is crucial. Since birth, IRIDA has been present, and it is typically identified in children. Iron values are abnormal when compared to conventional iron deficiency and suggest an illness. As in other cases of iron deficit, the percent saturation of transferrin is severely decreased (less than 10%); nevertheless, contrary to iron insufficiency, serum ferritin levels are normal or even elevated.³⁰ This is related to elevated hepcidin levels that cause storage iron sequestration, which result in increased ferritin accumulation in macrophages. None of the suggested tests for IRIDA diagnosis completely covers all instances. The genetic test identifies that *TMPRSS6* mutations, that in some cases (non-sense, frame-shift, and splicing mutations), are clearly causal. Functional investigations are required in other circumstances, such as for previously unreported missense mutations, in order to prove causation.³¹ These tests are, however, hard to come by. Independent of iron shortage, serum hepcidin levels are often elevated or normal, which is associated with high or normal ferritin levels. Concurrent C-reactive protein dosage is crucial to exclude inflammation.³² There is controversy about whether or not certain individuals with a phenotype of refractory iron deficiency who have a single mutant allele of *TMPRSS6* should be classified as having IRIDA. It is possible to imagine a range of situations, from the typical form of severe IRIDA caused by homozygous or compound heterozygous *TMPRSS6* mutations to enhanced vulnerability to iron shortage brought on by single mutations/polymorphic alterations.³³

Hepcidin normalisation on other iron parameters, like ratios of transferrin saturation (Tsat)/log hepcidin or Tsat/log Ferritin, is one method suggested to predict classic IRIDA.³⁴ Other publications claim that biallelic *TMPRSS6* mutations are present in the majority of individuals with a severe IRIDA phenotype and that, when unidentified, the second allele may be genetically occult. Subjects with a single allele often have a milder phenotype and react better to iron therapy than those with two mutations.³⁵ It's interesting to note that a number of *TMPRSS6* SNPs have been linked to blood donors' and some populations' susceptibility to iron deficiency. A 5-year-old female who was initially discovered to have an unusual IRIDA genotype with one *TMPRSS6* (I212T) causative mutation and one (R271Q) silent mutation has been reported to have a digenic inheritance.³⁶ Later on, she was identified as having the uncommon dominant condition Fibrodysplasia Ossificans Progressiva (FOP), which is caused by a mutant version of the *ALK2* gene in the BMP type I receptor gene *ACVR1*. Since the pathogenic allele *ALK2R258S* alters the gene's glycine-serine-rich region and makes the BMP/SMAD pathway too active by preventing it from binding its particular inhibitor FKBP12, it is constitutively active.³⁷ This unusual example is particularly instructive. First off, it has revealed a previously unknown function for FKBP12 as a regulator of liver *ALK2* and hepcidin because the *ALK2* glycine-serine-rich domain interacts with FKBP12 and the mutation destabilises the binding.³⁸ A connection between the activation of bone and liver BMP type I receptors has also been discovered as a result. Third, as no IRIDA was seen among additional FOP patients with the same *ACVR1* mutation and likely normal *TMPRSS6*, the case supports the role of intact *TMPRSS6* in regulating hepatic BMP/SMAD signalling.³⁹ Last but not least, this case supports the idea that *TMPRSS6* haploinsufficiency cannot result in classic IRIDA. The best method of treating IRIDA is not known. Since it is not absorbed, oral iron is useless. Vitamin C is added to enable variable response. In contrast to individuals with acquired iron insufficiency, intravenous iron typically results in a partial response at a slower rate. In most situations, EPO is ineffective.⁴⁰

PREGNANCY AND ANEMIA

The most typical hematologic issue during pregnancy is anaemia.⁴¹ Pregnancy-related physiologic anaemia is a dilutional process brought on by an increase in plasma volume. Plasma volume rises from 25% to 80% during a typical pregnancy.^{42,43} The increase starts at 6 weeks into the pregnancy and lasts until 24 weeks, after which there is a slower increase.⁴³ The weight of the foetus is directly related to the rise in plasma volume.^{43,44} In women who do not take additional iron, the erythrocyte mass also rises during pregnancy, increasing by 180–250 ml, or 10%–20% more than usual.⁴⁴ When iron supplements are used, the increment is between 350 and 450 ml, or around 30% more than usual. Erythropoietin production is enhanced, which causes the erythrocyte bulk to rise.⁴⁵ The hematocrit decreases three to five points during the first half of pregnancy as a result of the disproportionate rise in plasma volume relative to erythrocyte mass. However, as the pregnancy progresses, the plasma volume rises more slowly, which causes a little increase in hematocrit in women who are taking iron supplements.⁴⁶ Maximum hemodilution occurred between 23 and 26 weeks of pregnancy, according to the results of the current study's analysis of the haemoglobin, hematocrit, and erythrocyte counts in the iron-treated women. The impact of an iron-deficient erythropoiesis, which was overlaid, obscured the hemodilution effect in the placebo-treated women. We generated reference curves for haemoglobin throughout typical pregnancy in placebo-treated and iron-treated women separately due to the stark disparities in hematologic markers. An example haemoglobin reference curve for iron-treated women^{47,48} which both employed manual analytical techniques. In contrast to the curve, the Hytten and Lind haemoglobin curve is shaped differently. When compared to the current curve, earlier pregnancy was associated with higher mean haemoglobin values, while later pregnancy was associated with lower mean haemoglobin values, which were similar at 20 weeks of gestation, or 120 g/L. Three longitudinal investigations utilising Coulter S analysis on haemoglobin and erythrocyte indices in healthy pregnancies have been reported⁴⁸. These studies looked at hematologic indices in about 90 women with and without iron supplementation, although the amount of iron was not specified. Our mean haemoglobin readings were marginally, but consistently, higher than their findings throughout the whole pregnancy in both the placebo-treated and the iron-treated women. Hemoglobin concentration in 113 pregnant women who were given 100–200 mg of iron daily starting in the early stages of pregnancy.⁴⁹ A second-degree polynomial equation was used to quantitatively characterise the fluctuations in haemoglobin, and a smoothed reference curve was created. The mean haemoglobin levels on Koller's curve are somewhat lower than those on our iron-treated women's curve and almost identical to those on our placebo-treated women's curve. Hematologic markers during pregnancy in 22 iron-treated and 23 placebo-treated women who had been given 200 mg of iron daily starting in the first trimester. Their haemoglobin graph is confusing, and they don't give precise numbers. The mean haemoglobin of the iron-treated group, however, was 128 g/L at term, which is comparable to our measurement in iron-treated women. Authors have utilised discriminating haemoglobin levels in pregnancy ranging from 100-114 g/L in clinical studies[50]. A cut-off value of 110 g/L is commonly used in iron-rich women. We present values for women taking supplementary iron and those not taking it separately. According to the research, 12% of the women who received a placebo had haemoglobin levels of 110 g/L and serum ferritin levels of 12 mg/L, which are indicators of iron deficiency anaemia in pregnancy. The pregnant women who do not take supplementary iron, iron deficit and iron-deficient erythropoiesis are very common. In contrast, it was noted that the present study's iron-treated ladies did not have iron deficiency anaemia. We believe that iron deficiency anaemia during pregnancy is an unphysiological occurrence, and we propose that the discriminatory standards for "normality" be derived from a population of women who have received iron therapy and who are iron-replete. Women assigned to the iron therapy in the current trial had all started taking iron at 20 weeks of pregnancy[51]. The cut-off value for haemoglobin in iron-treated women during the first trimester should be 111 g/L when the 5th percentiles were chosen as the discriminating value for anaemia. For the first, second, and third trimesters of the second trimester, the cut-off levels were 109 g/L, 106 g/L, and 103 g/L, respectively. Cut-off values for the third trimester were 105 g/L for the first two thirds and 110 g/L for the final third. The lowest "normal" haemoglobin level should be 100 g/L throughout pregnancy, which is similar to the lowest discriminatory value in the second trimester in iron-treated women in our research.⁵² The haemoglobin and hematocrit values in the CDC Pregnancy Nutrition Surveillance System are used by the Centers for Disease Control (CDC) in the United States.⁵³ The results from four Western European studies on healthy pregnant women who used iron supplements between 1975 and 1982 are fairly similar to those from the current research. These levels were measured using manual analytical methods on women who were taking 100-200 mg of iron daily. The 5th percentile haemoglobin concentration in iron-treated women at eight weeks postpartum was 123 g/L, which is similar to the discriminating anaemia threshold of 120–121 g/L used in non-pregnant women.⁵⁴ After delivery, the stimuli for an increased erythropoiesis and enlarged plasma volume fade.⁵⁵

Iron Deficiency Vs Iron Deficiency Anemia

Depleted iron reserves are shown by iron deficiency (ID). The absence of stainable reticuloendothelial iron on a bone marrow specimen is the "gold standard" for identifying ID, although in clinical practise, it is typically identified by substitute laboratory indicators as a low serum ferritin or a reduced percentage of transferrin saturation by iron.⁵⁶ Below is a discussion of these parameters' values. The prevalence of ID in pregnancy is due to both the high prevalence of ID in premenopausal women as well as the iron needs of pregnancy. Depending on the population under study and the particular parameter used to establish ID, different estimations apply. The following discussion covers various diagnostic standards for ID during pregnancy. In a recent research from the USA that used either low serum ferritin (30 g/L) or low transferrin saturation (19%) to define ID, 42% of women who were not anaemic and were randomly chosen in the first trimester matched the lab criteria for ID.⁵⁷ The incidence of ID may vary depending on the patient group. In the US Third National Nutrition and Health Examination Survey (NHANES)⁵⁹, at least 25% of women aged 15 to 39 who participated were iron deficient, using a serum ferritin cut-off of 20 to 30 g/L to indicate ID or minimum iron reserves.⁵⁸ The Latina women in this age group had an iron deficiency rate of 50%, whereas the subgroups of African-American and non-Latina white women approximated the total survey population. 40–55 percent of premenopausal women were found to be iron deficient in a review of research from Europe⁶⁰. In most cases, an imbalance between dietary iron consumption and physiologic blood loss from menstruation or a recent pregnancy causes ID in premenopausal women. This imbalance may be exacerbated in

women who consume a vegetarian or vegan diet and do not take an iron supplement or who have iron malabsorption.⁶¹ Menstrual blood loss can represent 25–50 mg iron per cycle⁶² depending upon the patient's Hct/Hb concentration and the individual pattern of menstruation, and can be substantially greater in patients with menorrhagia. This is distinct from the situation for men and for postmenopausal women, in whom ID is a consequence of blood loss from a pathologic lesion, most commonly in the gastrointestinal tract, and where an endoscopic investigation for a source of blood loss is required. When iron reserves are depleted but the continued iron deficiency is not severe enough to result in a lowered Hb concentration, ID can exist without anaemia. Compared to healthy males, healthy women are far more likely to be in this state. In a research that established the typical range for serum soluble transferrin receptor concentrations, only 1.5% of males and 9.5% of healthy adult female volunteers (premenopausal and postmenopausal) had ID with normal blood counts. As was already mentioned, 42% of non-anemic pregnant women in the first trimester of the research were iron deficient. The clinical importance of ID without anaemia is a topic of ongoing investigation.⁴² ID without anaemia is typically a transitory stage. IDA follows phases that have been well-established for many years and arises when iron intake is insufficient to fulfil the ongoing demands for red cell formation. Iron-deficient erythropoiesis, or occasionally iron-restricted erythropoiesis, is the term used to describe the early phase. When there is sufficient stored iron but cytokine-driven hepcidin synthesis hinders iron mobilisation due to chronic disease/inflammation, this phrase is also used to describe erythropoiesis.⁶⁴ The Hb concentration and Hct gradually decrease in the early stages of iron-deficient erythropoiesis, but the morphology of the erythrocytes is normal. Serum iron concentration, total iron binding capacity (TIBC), transferrin concentration, and ferritin concentration are now reduced in the biochemical assays. As mentioned above, the patient may continue to have iron deficient erythropoiesis if iron intake is enough to keep the Hb/Hct and daily losses stable. Otherwise, unmet iron needs lead to a fall in Hb of 1-2 mg/dL (which may still be within the Hb normal range), a decrease in mean corpuscular volume (MCV), or the size of the average erythrocyte, and other symptoms. Soon after, the mean corpuscular Hb concentration, or MCHC, of the erythrocyte also starts to decrease. The persistent iron shortfall determines how quickly these changes take place and how quickly we move toward IDA. The morphologic manifestation of IDA is characterised by diminished MCV (microcytosis) and decreased MCHC (hypochromia) processes.⁶⁵

Requirements Of Iron In Women During Pregnancy

It is more difficult than it first appears to evaluate the effect of maternal ID on pregnancy course and on early children development. ID is more prevalent in groups who are economically and socially disadvantaged, and these difficulties may independently cause issues with pregnancy and early childhood development. In the case of IDA, it may be unclear if any unfavourable effects are anemia's typical side effect or are unique to ID. In a recent study, maternal IDA appeared to predict infant ID at six months of age in women who had contracted schistosomiasis while pregnant.⁶⁶ ID may serve as a flag for other dietary problems. According to a Pakistani research, early-pregnant underweight women had lower blood ferritin concentrations than either moms of normal or overweight weight. The most prevalent nutritional shortfall worldwide is iron insufficiency. Iron is a vital micronutrient that is necessary for the transfer of oxygen, energy metabolism, cognitive function, and blood cell production and cell division. affects nations with low, moderate, and high incomes, Up to one in four pregnant women in the UK are believed to be iron deficient. Iron Deficiency Risks and Effects on Mother and Baby for the Mother: Anaemia reduction in ferritin levels and iron reserves impaired synthesis of haemoglobin, increased susceptibility to and severity of infections, anaemia during pregnancy.⁶⁷ inadequate productivity and poor mental capacity Maternal mortality and morbidity at an increased risk, SOB, palpitations, depression, and exhaustion Low spirits Baby Infant Iron Deficiency Irritability (in the first 3 months of life), underweight at birth, early birth, anomalies arising at birth, cognitive dysfunction, risk of prenatal death and morbidity 20 years and younger, Eating disorder, digestive disorder (IBS, celiac), Vegetarian/vegan diet restrictions.⁶⁸

Approach to Iron Administration in Pregnancy

Obtaining Enough Iron Through Diet •More individuals are following restrictive diets, Diet alone will not restore levels if a pregnant woman is deficient; her ferritin reserves will be depleted; women may become deficient between booking and re-check; A lot of women require additional iron supplements. Traditional oral vitamins are plentiful, affordable, and readily available as supplements. Constipation, GI problems, side effects, and non-compliance are examples of common issues. Some "Iron Supplements" have very little iron in them, and bioavailability varies greatly amongst iron compounds and elements. Iron is also absorbed by a carrier mechanism (DMT -1). Iron deficiency anaemia during pregnancy has serious health repercussions for both the mother and the unborn child, and high dose oral treatment increases side effects. - If it doesn't work, an uncomfortable, expensive, and difficult treatment for the mother and the healthcare provider is IV iron. Supplementation for prevention can cut down on maternal anaemia at term by 70%.⁶⁴ Optimisation of health is the answer Prevention is preferable to cure. A growing amount of research indicates that taking supplements of lower doses of iron may be important. preventing the shortage in the first place, ensuring that iron reserves can handle the rise in demand brought on by pregnancy, have higher compliance results from fewer side effects. Midwives have a crucial role in the spread of information. Booking FB Cat for 28 weeks, Women who are at higher risk of deficiency but are not anaemic should have their serum ferritin levels tested. pregnant women at risk of iron deficiency, low iron reserves prior to conception, previous insufficiency history, Age, a pre-existing blood disorder (such as sickle cell or thalassemia).⁶⁸

CONCLUSION

The majority of expectant individuals can take oral iron, especially when it is administered once daily or on an irregular basis. However, intravenous iron treatment is secure and efficient if the patient is refractory to oral iron or unable or unable to consume iron orally. The simultaneous and quick correction of Hb/Hct and iron storage is one benefit of intravenous iron treatment. The average total amount of elemental iron to be injected intravenously is 1000–1500 mg. Endoscopic examination of the

gastrointestinal tract in premenopausal women with ID is unlikely to reveal a lesion responsible for blood loss in the absence of gastrointestinal signs or symptoms.

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