European Journal of Molecular & Clinical Medicine
ISSN 2515-8260 Volume 08, Issue 3 , 2021

Review: The Effect Of Iron Homeostasis During Pregnancy On Maternal And Fetal Body

Ali Jabbar Abdulhussin[1], Shihab Hattab Mutlag[2], Mahmood Kahtan Salih[3], Abdul-Hafeed H. Abdul-Wahab[4].

[1,2,3]College of Pharmacy/ University of Baghdad/ Department of pharmacology and toxicology/ Iraq.

[4]College of Pharmacy/ University of Baghdad/ Department of pharmaceutical Chemistry/ Iraq.

Abstract:
Millions of people suffer from iron deficiency which can lead to anemia annually. Most of those population are low income, and poor diet intake which leads to health and function implications. Interestingly, woman and particularly pregnant female are increase their demand for iron supplement to avoid the serious health consequences on their body and fetus. The iron deficiency and anemia have a great risk on pregnant women and fetus heath which can induce many health defects during perinatal period. On the other hand, the excessive iron level in the mother body can lead to Fenton reaction and generation of free radical which can damage fetus tissue specially in brain, liver and kidney. Therefore, adjusting iron dose and level during pregnancy are a crucial medical intervention to avoid multi organ damage either by deficiency or excessive intake of iron. In this review, iron metabolism and its effect on mother and fetus health will be discussed with the appropriate intervention to control the low and high level of iron during pregnancy.

Introduction:

An estimated 2150 million people are iron deficient, with deficiency severe enough to cause anemia in 1200 million people globally. Widespread particularly among tropical low-income populations, anemia has serious health and functional consequences. Due to their increased iron demands of menstruation and pregnancy, women of fertile age and pregnant-lactating women are especially affected by anemia and iron deficiency. Approximately 47% of non-pregnant women and 60% of pregnant women worldwide have anemia, while those who are iron deficient without anemia may comprise 60% and 90%, respectively. The anemic pregnant woman is at greater risk of death during the perinatal period. Iron deficiency also affects performance during pregnancy and delivery, lactation performance, working capacity and general well-being, and immunity status. Infants are adversely affected in terms of health, development, hematological status, and iron nutrition. Most anemia is, however, the result of severe iron deficiency, and therefore open to prevention and treatment interventions with a very high benefit/cost ratio. Accordingly, world authorities have agreed that anemia in pregnant women must be reduced by one-third by the year 2000. The author recommends expanding the target for iron supplementation to all women of fertile age who might become pregnant, the adoption of a preventive instead of therapeutic approach to iron deficiency, and the exploration of new supplementation programs. [1]

Primary focuses have been to increase the amount and bioavailability of iron in the diet, to control infections that contribute to iron losses from the body, and to improve economic, educational, and social conditions that contribute to the high prevalence of iron deficiency. New diagnostic tools are being developed to increase the sensitivity and accuracy of iron deficiency detection in field settings with the hope that improved detection will produce more effective interventions. Nutritional iron deficiency is highest in population segments that are at peak rates of growth, namely, infants, young children, and pregnant women. Pregnancy is a time in which the risk for developing iron deficiency anemia is highest, because iron requirements are substantially greater than average absorbable iron intakes. Physiologic demands for iron increase from 0.8 to ≤ 7.5 mg absorbed Fe/day, although there is considerable debate about the exact upper limits of this increased iron demand in the third trimester of pregnancy. Such demands result in a decline in iron stores during pregnancy and ultimately can produce iron-deficient erythropoiesis and anemia because a positive or even neutral iron balance is difficult to attain. The median need for iron in the second and third trimesters of pregnancy is calculated to be nearly 4.6 mg Fe/day, whereas the 90th percentile is 6.7 mg Fe/day. These calculations are based on the estimation that the median iron need during pregnancy is 840 mg, with a 90th percentile of 1210 mg. If the iron needs for 6 months of lactation are considered,the median total iron requirement would be 1018 mg absorbed Fe. This calculation translates into an additional median need of 426 mg iron for this 15-months period. [2]

The decline in iron status that normally accompanies pregnancyresults in an increase in the efficiency of absorption ofdietary or supplemental iron. However, there is a significantdiscrepancy between these 2 reports regarding the magnitudeof the increase in iron absorption. As a result, it is uncertainwhether pregnant women can “naturally” attain a neutral iron balancewithout the need for supplemental iron. Some scientistsargue that it is not possible to maintain the iron status of a pregnantwoman with normal dietary practices and that iron prophylaxisis necessary. The worldwide anemia prevalence datasuggest that normal dietary intakes of iron are insufficient to meet peak daily requirements for a significant proportion of pregnant women. In the industrialized world, estimates suggest that ≥ 30% of pregnant women will have depleted iron stores by the end of pregnancy, and in some population groups (eg, adolescents) depleted iron stores could occur in ≥ 80% of the population. In the developing world, these estimates are higher. For example, 47% of pregnant women in Africa, 39% of pregnant women in Latin America, 80% of pregnant women in SoutheastAsia, 65% of pregnant women in the eastern Mediterranean, and40% of pregnant women in the West Pacific are believed to beanemic. Worldwide, at least one-half of anemia cases occurringduring pregnancy are due to nutritional iron deficiency. Subclinicaliron deficiency is nearly as widespread as iron deficiencyanemia. Current control programs include supplementation, fortification, dietary modification, and parasitic disease control.[2]

The prevention of iron deficiency in pregnancy is desirable, because severe iron deficiency anemia (hemoglobin concentration of 90–100 g/L) in pregnancy is related to both impaired fetal and maternal health. At the anemia end of the hemoglobindistribution curve, birth weight is decreased, complications occur (e.g., toxemia, labor and delivery complications, small-for-gestational age infants), and maternal functioning is impaired. However, a modest drop in hemoglobin concentration in pregnancy appears to be a normal physiologic event; hemoglobin concentrations reach a nadir in the mid second trimester of pregnancy and then rise again in the third trimester. Maternal hemoglobin distribution and infant outcomes have a U-shaped curve, with an increased risk for infants whose mothers have either a very low or a very high hemoglobin concentration. Thus, the prevention of severe anemia appears desirable. It is less obviouswhether the prevention of a decline in serum ferritin during pregnancyis a necessary or

desirable dependent variable. Few functionaloutcomes, for either mother or baby, are associated directlywith depletion of iron stores alone; rather, the benefit derived isfrom an improvement in maternal and fetal iron stores.This can be a true long-term benefit for both mother and infantbecause the mother may enter her next pregnancy with better iron reserves and the infant may be weaned with a larger iron store. Anexception to this may be the neurologic development of theinfant. Animal studies of perinatal and early postnatal iron deficiencyclearly indicate that iron deficiency leads to alterations inbrain iron content, distribution, and metabolism. A recentreport from the International Nutritional Anemia ConsultativeGroup summarizes the extensive human literature on theadverse effects of iron deficiency in early life on mental performance.This report observes that iron deficiency in early life islikely to have negative consequences for normal neural developmentand functioning.[2]

The second major question posed in the preceding section is based on emerging knowledge that iron, in excess, is an active participant in the Fenton reaction, which results in the production of free radicals and oxidative damage. High single doses of iron as a fortification or as a dieta ry supplement may be associated with increased oxidative product formation and the initiation of various pathogenic processes such as cardiovascular disease, neuropathology, and cancer. Thus, the implications ofadding a large amount of fortification iron to a food consumed predominately by pregnant women, or the provision of a very large dose of supplemental oral iron, need to be reconsidered. [2]

The third major question posed concerns the timing of maternal iron deficiency and the greatest negative effect of the deficiency on fetal growth. Strong evidence shows that iron deficiency in the first trimester of pregnancy results in significant decrements in fetal growth, whereas iron deficiency anemia in the second and third trimesters has little effect on fetal growth. Most perinatal iron intervention programs rely on the initiation of treatment at the first visit of the newly pregnant woman to her health care provider, somewhere around 10–15 wk. of pregnancy. It is possible, however, that by this time the real window of opportunity for a positive intervention against iron deficiency has passed if fetal growth and development are the dependent variables considered. Perhaps targeting intervention programs to the prenatal period may be of a greater benefit than relying on intervention in the late first trimester or early second trimester of pregnancy.[2]

Iron:

Iron is a naturally occurring element found in the nature. It is denoted by the symbol Fe and has an atomic number 26. Iron is one of the most common metals occurring on earth. It occurs in a variety of oxidation states but out of all the states +2 and +3 are the most common states. Out of the two ferrous iron is absorbed better in the body than ferric iron and this is the reason it is used in many iron supplements. Iron occurs in the form of metal, oxides, organic and inorganic forms. It plays a crucial role in the formation of different complexes with oxygen in hemoglobin and myoglobin (oxygen transporters). Iron is widely used in preparation of foods and medicines, micronutrients for the plants and also has vast applications in the field of automobiles.it occurs in four distinct crystalline forms and dissolves readily in dilute acids. It is a very crucial component of different metalloproteins and plays a crucial role like oxygen sensing and transport, electron transfer and catalysis.1,2 Iron toxicity from intentional or accidental. [2]

ingestion is a common poisoning. Life-threatening toxicity is associated with pediatric ingestion of potent adult preparations, such as prenatal vitamins. Serious iron ingestion in adults is usually associated with suicide attempts. The exposure to iron can be in various forms including metal, salts (ferrous sulfate) and organic compounds. Organs that are affected by iron toxicity

are pancreas, liver, kidneys, central nervous system and joints. The clinical features of iron poisoning along with the appropriate diagnosis and treatment is extremely important in iron toxicity cases. [2]

Pharmacokinetics of Iron:

Absorption

Iron absorption is a complex process that occurs in the proximal small bowel and consists of a series of step. These include binding of the iron molecule to the brush border, uptake of bound iron into the intestinal mucosal cell, intracellular handling of iron, transcellular transport and passage of the iron from the cell into the portal circulation. In case of therapeutic dosing 10 - 35% is absorbed, but in iron deficiency this increases to 80-95%. Peak serum concentrations occur approximately 4 -6 h after the ingestion of an overdose. The absorption of iron is dependent on body iron stores, hypoxia and rate of erythropoiesis. Dietary absorption of iron takes place at duodenum and upper jejunum. [3]

Distribution

Distribution of iron is very rapid. Entry of iron into tissues is an active process involving specific transferrin receptors and endocytosis. Liver can passively absorb iron and this is one of the reasons. it is a target organ in iron poisoning. Half-life of iron after therapeutic dosing is approximately 6 hours as well as in case of overdose. [4]

Iron Metabolism During Pregnancy

Major changes in iron metabolism during pregnancy include the cessation of menses, expansion of the red blood cell mass by about 20%, and the deposition of substantial amounts of iron in the fetus and placenta. The expansion of maternal red cells is maximal around weeks 20 -25 of gestation and is probably responsible for the marked fall in serum ferritin concentrations that occurs between about weeks 12 and 15. Most fetal iron uptake occurs after week 30, during a time when maternal serum ferritin is fairly constant. Thus, fetal and placental iron needs are presumably met predominantly by increased efficiency of maternal iron absorption during the last 10 weeks of pregnancy. Total circulating serum transferrin increases by about 250% between conception and term, probably in response to estrogenic hormones. Fetal i ron is derived from maternal transferrin,which delivers iron to transferrin receptors on the apical surface of the placental syncytiotrophoblast (the layer of fused cells that separates the maternal and fetal circulations). [5]

Holotransferrin is endocytosed by these cells, and the apotransferrin is returned to the cell surface. The disassociated iron binds to ferritin in the placental cell, from which it is picked up by apotransferrin on the basolateral (fetal) surface of the cells, and enters the fetal circulation as holotransferrin. The amount of iron transferred across the placenta depends on two factors: the number of transferrin receptors on the apical (maternal) side of placental cells, and the concentration of ferritin in the cells. The number of transferrin receptors is increased if cellular iron is low and decreased if cellular iron is high. Ferritin synthesis by the placenta may prevent excessive iron transfer to the fetus. These two mechanisms help maintain a constant f low of iron from the mother to the fetus and reduce the risk of fetal iron deficiency or toxicity. However, as will be discussed, fetal iron stores probably do reflect maternal iron status to some extent. When fetal iron demand is high, such as for the increased hemoglobin synthesis by the fetus in diabetic pregnancy,the fetus may be able to mobilize its own iron stores to support erythropoiesis. [5]

Excretion:
Excretion of iron after an overdose is insignificant as the body doesn't have any effective means ofexcreting it from the body.[5]

Mechanism of Iron Action and Toxicity
Iron has the ability to produce oxygen free radicalsunder aerobic conditions. Overproduction ofreactive oxygen species such as superoxide andhydroxyl ion may lead to cellular damage. Organsexposed to high concentrations of iron are thegastrointestinal epithelium, cardiovascular systemand the liver. Five clinical phases are knownnamely- Gastrointestinal Toxicity, RelativeStability, Circulatory Shock and Acidosis,Hepatotoxicity and Gastrointestinal Scarring. [6]Symptoms of iron poisoning are evident mostlyafter 6 hours of administration through oral route.The amount of iron that may cause poisoningdepends on the age group and the mg/kgbodyweight. Symptoms may also occur in respectto the different available oral forms. After the earlysymptoms the serious complications may developwithin 48 hours after the overdose. [6]

Table 1: Normal/ Reference and Toxic values of Iron[6]

Matrixes	Normal level	Toxic level
Blood	**500-2000µg/l**	**more than 3500 µg/l**
Urine	**65µg/g**	**more than 65 µg/g**

Benefits of Maternal Iron SupplementationDuring Pregnancy :
Iron is necessary for both fetal/placental development and to expand the maternal red cell mass. Prevalence of iron deficiency in pregnant women in the US is estimated to be 19 percent, ranging from 7 percent in the first trimester to 30 percent in the third trimester. Iron deficiency is more prevalent among Mexican-American and non-Hispanic black pregnant women, and among grand multiparous women.[7]There are two dietary forms of iron: heme and non-heme. The most bioavailable form is heme iron, which is found in meat, poultry, and fish. Non-heme iron, which comprises 60 percent of iron in animal foods and all of the iron in plant foods, fortified grains, and supplements, is less bioavailable. Absorption of non-heme iron is enhanced by vitamin C-rich foods or muscle tissue (meats, poultry and seafood), and inhibited by consumption of dairy products and coffee/tea/cocoa.[7]
Experts recommend an increase in iron consumption by approximately 15 mg/day (to approximately 30 mg/day) during pregnancy to prevent iron deficiency anemia; this amount is readily met by most prenatal vitamin formulations and is adequate supplementation for non - anemic women. The CDC recommends that all pregnant women take a 30 mg/day iron supplement by the first prenatal visit. Intermittent iron supplementation (one to three times per week) appears to be as effective as daily supplementation for preventing anemia at term and is better tolerated.[8]

A 2015 systematic review for the United States Preventive Services Task Force observed that routine iron supplementation had inconsistent effects on a variety of pregnancy outcomes, but

noted a consistent reduction in the frequency of iron deficiency anemia at term (RR 0.29, 95% CI 0.17-0.49; four trials) [9]. There is no strong evidence that iron supplementation in non-anemic pregnant women improves maternal or child clinical outcomes, but iron is important in fetal brain development and it has been proposed that screening for and treatment of iron deficiency before anemia develops may benefit neurodevelopmental outcome. Women with iron deficiency anemia (first- or third-trimester hemoglobin [Hb] <11 g/dL or second-trimester Hb ≤10.4 g/dL and low serum ferritin [<40 ng/mL]) should receive an additional iron supplement (30 to 120 mg per day) until the anemia is corrected. One option is 65 mg of elemental iron (325 mg ferrous sulfate) every other day.[9]

Iron absorption decreases with increasing dose;thus, larger supplementation amounts are best split into several doses during the day. In women who do not tolerate oral iron, iron can be administered intravenously.[10]

Iron deficiency during pregnancy:

Iron deficiency is the second most common cause of anemia in pregnancy after physiologic anemia (which is not a pathologic condition).Several factors contribute to iron deficiency:Women in some parts of the world, especially in resource-limited settings, may have insufficient dietary Blood losses from previous pregnancies and/or menstruation, as well as a short interpregnancy interval, may lead to iron deficiency or borderline iron stores. Physiologic iron loss is approximately 1 mg per day in adults; women of childbearing age require additional daily iron to compensate for menstruation (approximately 0.8 mg/day). [11, 12]

Iron requirements increase dramatically through pregnancy due to the expanding blood volume of the mother and the iron requirements for fetal RBC production and fetoplacental growth. [11]Cumulative total requirements for expansion of the maternal RBC mass and fetal RBC production/fetoplacental growth are approximately 500 mg and 300 to 350 mg, respectively.In the first trimester, approximately 1 to 2 mg/day of iron is needed due to normal gastrointestinal sloughing and the early pregnancy-related increase in RBC mass [13].

By the second trimester, the demand increases to 4 to 5 mg/day due to requirements for increased maternal RBC production as well as fetal RBC production and fetoplacental growth.In the third trimester, the demand increases to approximately 6 mg/day due to ongoing maternal and fetal RBC production and fetoplacental growth.Delivery results in the loss of approximately 250 mg.Certain underlying conditions that preclude adequate iron intake or impair iron absorption can increase the risk of iron deficiency during pregnancy, especially if the woman has not received adequate supplementation. Examples include nausea and vomiting of pregnancy, inflammatory bowel disease, bariatric surgery (eg, gastric bypass), and other conditions. [13]

TheConsequences of Iron Deficiency on TheWell-being of the Mother and on The Growth of The Fetus

Maternal outcomes

A study by the World Health Organization (WHO) documented that severe antenatal or postnatal maternal anemia (of any type) was associated with an increased risk of maternal death.Other studies have observed that maternal anemia was associated with several adverse pregnancy outcomes such as maternal transfusion, antenatal/postnatal sepsis, cesarean delivery, and later cardiovascular disease. [14, 15]Maternal Weight Gain*:*Pregnancy weight gain was positively related tomaternal hemoglobin because low iron intake is usuallyassociated with a lower consumption of energyand other nutrients. Anemic mothersmay be less able to tolerate hemorrhagic bloodloss during childbirth and have a greater risk of infectionsand slow wound healing**.**[16]

Outcomes in the child:

Several large studies have found correlations between maternal anemia and the risk of preterm birth, low birth weight, and small for gestational age neonates. Correlations between maternal and cord-blood ferritin levels have been observed.A cohort study from Sweden involving over 500,000 children (with anemia in approximately six percent of gravidas) found that maternal anemia was associated with increased risks of autism spectrum disorder, attention deficit hyperactivity disorder, and intellectual disability in pregnancies when the anemia was identified in the first 30 weeks of pregnancy as compared with maternal anemia identified after 30 weeks or no maternal anemia. The cause of anemia was likely to be iron deficiency in the majority of cases, but this was not verified in the study, and other potential cofounders were not evaluated.[15]

A longitudinal study of 185 individuals who were followed from infancy to the age of 19 years found that those who had iron deficiency or iron deficiency anemia as infants for three or more months had impaired cognitive functioning compared with those who did not have iron deficiency. The gap in cognitive functioning was greatest in those of low socioeconomic status, but persisted even in those with high socioeconomic status. Other studies have documented correlations of maternal anemia with later cognitive defects. [15]

Animal studies have demonstrated a clear role for iron in normal brain development, dendritic growth, and synapse formation, as well as behaviors such as grooming, tasks requiring executive function, timidity, and poor spatial learning.Iron deficiencyanemia in infants and toddlers is associated withcomparatively poor performance on developmentalscaleswhich is improved by iron supplementation Iron in the brain is involved in the synthesisof neurotransmitters that affect human behavior**.**Iron deficiency reduces platelet monoamine oxidaseand the functional activity of D2 dopamine receptors.In animal models,behavioral development is also affected by iron deficiency with reduced motor activity and changesin the sleep cycle.Iron deficiency anemia is likely to affect themother's level of activity, attention, and motivation,and these effects could in turn affect the frequencyand duration of interaction with her infant.[16]

Iron OverdoseDuring Pregnancy:

Considering changes in maternal hematologicstatus only, there is no advantage of iron doses > 60 mg/dand perhaps no advantage of doses > 30 mg/d. Thenumber of side effects increases dramatically when the dose ofiron increases. In an Indian study, 32%, 40%, and 72% of womenexperienced side effects as the iron dose rose from 60 to 120 to240 mg Fe/ d. respectively. Thus, dose and composition ofthe iron supplement clearly affect maternal outcome and mayprovide an alternative to the therapeutic high-dose approach.Another alternative to high therapeutic doses of iron is to providea delayed-release form of oral iron that would producefewer side effects but still provide the iron necessary to meetphysiologic needs. In such formulations, iron is released ata slower rate because of the action of gastric acid on the matrixcontaining the ferrous sulfate, thus reducing the bolus load ofiron into the gastrointestinal system.[17]

In a study with a loosely controlled design that included interventionsfor variable periods of time, Ridwan et al examined120 mg Fe as ferrous sulfate given weekly compared with 60 mgFe given daily in women during the second and third trimesters of pregnancy. The intervention interval was between 8 and 20 wk,with all interventions starting at the first prenatal clinic visit andconcluding at the 30th week of pregnancy. Initial and final hemoglobinconcentrations in the 68 women supplemented daily withiron that were not significantly different from the hemoglobinconcentrations of the 71 women supplemented weekly. However,the weekly dose of iron was insufficient to keep serum ferritinfrom decreasing slightly. The anemic women in both treatmentgroups responded equally to supplementation, thus showing noparticular benefit of daily iron supplementation. [17]

Iron supplement During Pregnancy:

Iron plays an extremely crucial role in normal human physiology; it is involved in oxygen transport and the regulation and differentiation of cell growth.[18, 19] Iron supplementation is considered necessary during pregnancy. Due to increasing blood volume, fetal growth and depletion of vitamins, minerals and metabolic cofactors, diet alone may not provide enough necessary elements for proper growth. Iron containing supplements are often thought of as benign and are readily available in many forms through retail stores and prescriptions. Unfortunately, iron was reported to be one of the most widely overdosed medications in pregnant women along with analgesics (particularly acetaminophen), sedatives, antibiotics, and antihistamines. It is important for the clinician to recognize the dangers of iron over use and to understand patient management in an overdose situation, especially in pregnancy.[20, 21]

Export of Iron to The Fetal Circulation:

Iron is exported from the placental syncytiotrophoblasts to the fetus through the iron exporterferroportin, located on the basal (fetal-facing) membrane of the placental syncytiotrophoblast.In human placentas from iron-sufficient non-anemic pregnancies collected between weeks 24 and 40,
placental FPN expression increased with gestation age. In mice, early in pregnancy FPN was shown to be expressed in the exVE, a cell layer responsible for early nutrient transport, and later in thesyncytiotrophoblast (likely SynT-II layer). Global knockout of FPN in mice was embryonic lethal however, when FPN expression was preserved in only the exVE and placenta, embryo development wasrescued, confirming an essential and non-redundant role of FPN in placental iron export. Followingexport through FPN, the immediate fate of iron is unclear.[22]

Exoplasmic ferroxidases may oxidize exported ferrous iron to ferric iron for loading onto fetaltransferrin. FPN transport function is facilitated by the presence of ferroxidases, although in vitrostudies have also demonstrated function in the absence of ferroxidases. In order to facilitate ironexport across basal membrane of the syncytiotrophoblast to the fetal circulation, the ferroxidases wouldneed to be produced by the syncytiotrophoblast itself or by the fetus. All three known mammalianmulti-copper ferroxidases, ceruloplasmin, hephaestin and zyklopen, were localized by immunohistochemistry to the placenta.[22]

.

Once iron is exported across the basal side of the syncytiotrophoblast through ferroportin, iron still needs to cross the fetal endothelium to reach fetal circulation. This process is not understood.Iron exported through ferroportin may be loaded onto transferrin, whose concentrations in fetalcirculation gradually increases during gestation. Fetal transferrin is produced by the fetal liverand possibly some other organs. However, NTBI is also found in fetal circulation, at least in the firsttrimester, when transferrin concentrations are relatively low and transferrin saturation in the fetalcirculation is high. NTBI appears to be able to support fetal development. [22]

Regulation of placental iron transport:

Placental iron transport may be regulated by maternal, placental and fetal signals. A commonmisconception is that the fetus is a "perfect parasite", able to acquire adequate iron irrespective of the
mother’s iron status. However, several human and macaque studies confirmed that neonatal ironstores are compromised when the mother is iron-deficient or anemic. Understanding of theregulation of placental iron transport should improve the prevention and treatment of fetal irondeficiency and anemia.[22]

Maternal Iron Availability:

Transfer of iron across the placenta to the fetus is dependent on the bioavailability of iron in thematernal circulation. Iron absorption during pregnancy increases with gestational age. Additionaliron needs are met through mobilization of liver and spleen iron stores. These systemicadaptions are mediated at least in part by maternal hepcidin. Hepcidin functionally inhibits major flowsof iron into the circulation from macrophages recycling senescent erythrocytes, duodenal enterocytesabsorbing dietary iron, and hepatic stores. Thus, bioavailable iron levels in plasma inverselycorrelate with hepcidin levels. Hepcidin expression is regulated by plasma iron concentrations, body ironstores, infection and inflammation, erythropoiesis and pregnancy. During pregnancy,maternal hepcidin levels decrease to nearly undetectable levels in the second and third trimesters ofhuman pregnancy and in the third week of pregnancy in rats, presumably to maximize ironbioavailability and enhance transport across the placenta. In fact, one study demonstrated a negativecorrelation between maternal hepcidin concentration (albeit measured at delivery) and net dietarynonheme and heme iron that was transferred to the fetus (as determined by stable iron isotopes).[22]

The mechanism of maternal hepcidin suppression is currently unknown, but maternal iron status contributes to hepcidin regulation during pregnancy, with iron deficiency resulting in a more profoundhepcidin suppression.In developed countries, most women are iron-replete. Extensive use of maternal iron supplements inthis population raises the possibility that in some pregnancies, the placenta may be exposed to high ironconcentrations. Whether this has an effect on placental function is unclear. Excess free iron is known tocatalyze generation of free radicals and cause tissue damage in disease of iron overload. It remains to bedetermined whether the placenta can become iron-loaded in different pathological states or due to ironsupplementation in pregnancy, and whether this iron load is sufficient to increase placental oxidativestress to such a degree as to cause placental damage. Large epidemiological studies have demonstrateda U-shaped association between the iron marker ferritin and the risk of adverse pregnancy outcomes,including preterm birth and impaired fetal growth. However, association of high ferritin withadverse outcomes may not only be related to high iron, but also to inflammation or a combination ofthe two. Any direct effects of iron excess on the placenta remain to be elucidated.[22]

Fetal and Placental Regulation:

In addition to maternal hepcidin regulating iron bioavailability in maternal circulation, fetal hepcidin could determine the rate of placental iron transfer to the fetal circulation through regulation ofplacental FPN. Placental FPN localizes to the basolateral side of syncytiotrophoblasts and is thusaccessible only to fetal and not maternal hepcidin. Increased fetal hepcidin, either as a consequence oftransgenic hepcidin overexpression or mutations in the hepcidin regulator TMPRSS6, was able to regulate placental ferroportin, resulting in severe fetal iron deficiency and even death. However,under normal physiological conditions, animal studies have demonstrated very low levels of fetalhepcidin. This is suggestive of a minimal role for fetal hepcidin in regulating placental FPN inhealthy pregnancy. In humans, cord blood hepcidin has been assessed; however, because ofthe stress of delivery, these levels likely do not reflect fetal hepcidin concentrations. Indeed, in mice,hepcidin levels transiently increase immediately after birth, between post-natal day (P)0 and P2.[22]

In addition to the iron availability in maternal circulation, the amount of iron transferred to the fetus willdepend on the expression levels of iron transport proteins in the placenta. Iron transporters appear tobe regulated in response to maternal iron status, presumably mediated by the alterations in the ironconcentrations in the placenta itself. Maternal iron deficiency in rats increased TFR1 and

DMT1expression in the placenta but not *Fpn* mRNA (91). This is consistent with the role of cellular ironregulatoryproteins 1 and 2 (IRP1 and 2), which post-transcriptionally regulate iron uptake, storage andexport proteins. Briefly, during cellular iron deficiency, IRPs bind to 'iron response elements' (IREs)within UTRs of iron-related genes. Binding of IRPs to 3' IREs promotes stabilization of mRNAs involved inincreasing iron uptake (i.e. TFR1), whereas binding to 5' IREs prevents translation of mRNAs involved iniron storage and export (i.e. ferritin and FPN). [22]

Both IRP1 and IRP2 activity have beendetected in human placentas. In one study, in placentas from diabetic and non-diabeticpregnancies, iron-deficient placentae had higher placental IRP1 activity and increased expression of*TFR1* mRNA (93). Another study in iron-replete non-anemic mothers found an inverse correlationbetween cord blood ferritin and placental IRP1 and 2, suggesting that fetal iron status may also affectplacental iron regulation. IRP regulation of placental FPN is less clear. [22]

Pathophysiology of Iron Overdose:

As a transition metal, iron is highly involved in the reduction-oxidation reaction. Iron readily shifts from the ferric (Fe3+) to ferrous (Fe2+) state by accepting and donating electrons. Between the two different forms of iron, ferric and ferrous, ferrous is better absorbed in the gastrointestinal tract, particularly in the duodenum. Via transferrin (transported iron) and ferritin (stored iron), the absorption of iron is closely regulated.[21]

In an overdose situation, initial symptoms and tissue damage occur in the gastrointestinal epithelium. Systemic toxicity begins once iron-induced reactive oxygen species enters the circulation. When serum transferrin becomes saturated, "free" iron circulates to various organ systems and promotes oxidative damage. Elevated iron concentrations can be detected in the stomach, liver, brain, heart, lung, small bowel, and kidney. These findings are consistent with presentations observed in patients with severe iron toxicity. In addition, iron toxicity can lead to intracellular damage causing disruption of mitochondrial oxidative phosphorylation. This may promote a shift towards anaerobic metabolism placing the patient in a state of metabolic acidosis which may further contribute to harm. Iron toxicity can also cause excessive post arteriolar dilation, increased capillary permeability, and coagulopathy which may lead to severe acidosis and shock. During pregnancy, the fetus does not seem susceptible to high maternal serum iron loads; nor have fetal malformations been associated with iron overdoses. Animal and human data demonstrate no increased iron loads in fetal circulation or in umbilical cord blood.[21]

Management of Iron Overdose During Pregnancy and Save Fetus Life:

Pregnancy should not delay or preclude therapy when an iron overdose is suspected. Maternal danger and toxicity should receive immediate evaluation, studies, and therapy. Fears of potential teratogenicity should not interrupt initiation of such treatment, as fetal safety is dependent on maternal health. Presentations may vary widely as symptoms may differ based on time of ingestion, amount and type of iron pills ingested, as well as if there were any significant coingestants involved in the situation. The patient will likely require intravenous volume repletion and supple- mental oxygen. If necessary, patient may require intubation to keep the airway patent and prevent aspiration. Results of laboratory values such as arterial blood gases, complete blood counts, metabolic panels, coagulation panel, and hepatic profile should further assist in developing supportive care strategies. [23,24]

Abdominal Radiograph:

Abdominal radiograph may be considered for the purpose of visualizing radio opaque iron tablets. Radio opacity may vary by form of iron supplement ingested, time since ingestion, and amount of elemental iron ingested. Oral iron formulations can conglomerate in the gut to form a

solid mass or bezoar. Such formation can further complicate the toxicity as it can serve as a reservoir for iron and result in variable, continuous iron release. Radiographic findings may be particularly helpful in guiding and evaluating the success of treatment. Should the clinician believe an abdominal radiograph is warranted, pregnancy should not preclude this evaluation. The American College of Radiology states that pregnancy is a relative contraindication to ionizing imaging modalities. A single diagnostic X-ray procedure does not result in a radiation dose adequate to threaten the well- being of the developing pre-embryo, embryo, or fetus. The American College of Obstetricians and Gynecologists agrees with this position.[23,24]

Gastrointestinal Decontamination:

Upon stabilization of the patient, gastrointestinal decontamination strategies should be considered to promote excretion and limit further iron absorption. Although several methods may be employed, whole bowel irrigation (WBI) has consistently shown efficacy against iron ingestions.[24]Gastrointestinal decontamination strategies used for iron toxicity have previously included induced emesis, activated charcoal, and orogastric lavage. In the case of iron toxicity, these strategies have been proven ineffective and some are considered unsafe.

WBI is an effective, safe, and non-invasive gastrointestinal decontamination modality for management of iron toxicity. Van Ameyde et al. have reported a successful management of iron toxicity in a pregnant woman during her third trimester. Using an osmotically balanced polyethylene glycol electrolyte lavage solution (PEG-ELS), WBI prevents further iron absorption by inducing a liquid stool. Because PEG solution contains balanced electrolytes, WBI with PEG can result in resolution of electrolyte imbalance. Various PEG-ELS formulations are available and may differ slightly in electrolyte content.[25]

Deferoxamine:

Deferoxamine is a chelating agent that exhibits high affinity and specificity for iron, does not cross the placenta and is safe for use in pregnancy. It has been found that deferoxamine easily chelates iron from ferritin, hemosiderin, and transferrin. Conversely deferoxamine does not bind or remove iron from hemoglobin or the cytochrome enzymes. Deferoxamine may chelate intracellular extramitochondrial iron. There are several presentations that may necessitate immediate initiation of deferoxamine therapy. If presence of metabolic acidosis, repetitive vomiting, lethargy, hypotension, or signs of shock. If the serum iron concentration is greater than 400 mcg/dL or if more than 20 mg/kg elemental iron is ingested, deferoxamine therapy should be initiated. [26]

Conclusion:

Acute iron toxicity in pregnancy is a medical emergency that can result in multi-system organ failure leading to maternal death and potential fetal demise. A thorough evaluation of the patient including time of ingestion, form of iron supplement ingested, and time of symptom development are important. Calculating the amount of elemental iron ingested is also critical in determining treatment strategies. High maternal serum iron loads do not affect the developing fetus and are not associated with fetal malformations; however advanced poisoning can lead to maternal death, spontaneous abortions or pre- term emergency deliveries. Initial treatment strategies may include supportive care management and the removal of iron from the body using whole bowel irrigation with PEG-ELS. Deferoxamine treatment along and potential surgical interventions are also modalities that may be employed in more serious cases. Despite concerns of teratogenicity deferoxamine does not cross the placenta and is regarded as safe for use during pregnancy. Maternal resuscitation must always be the primary objective in acute iron overdoses and, therefore such concern should not delay clinically indicated maternal treatment.

Reference:

1. Viteri FE. The consequences of iron deficiency and anaemia in pregnancy on maternal health, the foetus and the infant. SCN news. 1994(11):14.
2. Beard JL. Effectiveness and strategies of iron supplementation during pregnancy. The American journal of clinical nutrition. 2000 May 1;71(5):1288S-94S.
3. Parikh's Textbook of Medical Jurisprudence, Forensic Medicine & Toxicology, 6th ed. CBS Publishers & Distributors, New Delhi, 2005:9.15
4. Zhang D, Meyron-Holtz E, Rouault TA : Renal iron metabolism: transferrin iron delivery and the role of iron regulatory proteins. J Am Soc Nephrol 2007; 18: 401-406.
5. Starreveld JS, Kroos MJ, van Suijlen JD, et al. Ferritin in cultured human cytotrophoblasts: synthesis and subunit distribution. Placenta 1995;16:383-95
6. Schulz M., Schmoldt A: Therapeutic and toxic blood concentrations of more than 800 drugs and other xenobiotics. Pharmazie 2003 ; 58: 447-474.
7. Mei Z, Cogswell ME, Looker AC, et al. Assessment of iron status in US pregnant women from the National Health and Nutrition Examination Survey (NHANES), 1999-2006. Am J Clin Nutr 2011; 93:1312.
8. Peña-Rosas JP, De-Regil LM, Dowswell T, Viteri FE. Intermittent oral iron supplementation during pregnancy. Cochrane Database Syst Rev 2012; :CD009997.
9. Stoffel NU, Cercamondi CI, Brittenham G, et al. Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: two open-label, randomised controlled trials. Lancet Haematol 2017; 4:e524.
10. Froessler B, Collingwood J, Hodyl NA, Dekker G. Intravenous ferric carboxymaltose for anaemia in pregnancy. BMC Pregnancy Childbirth 2014; 14:115.
11. Bothwell TH. Iron requirements in pregnancy and strategies to meet them. Am J Clin Nutr 2000; 72:257S.
12. Daru J, Zamora J, Fernández-Félix BM, et al. Risk of maternal mortality in women with severe anaemia during pregnancy and post partum: a multilevel analysis. Lancet Glob Health 2018; 6:e548.
13. Drukker L, Hants Y, Farkash R, et al. Iron deficiency anemia at admission for labor and delivery is associated with an increased risk for Cesarean section and adverse maternal and neonatal outcomes. Transfusion 2015; 55:2799.
14. Tunkyi K, Moodley J. Anemia and pregnancy outcomes: a longitudinal study. J Matern Fetal Neonatal Med 2018; 31:2594.
15. Wiegersma AM, Dalman C, Lee BK, et al. Association of Prenatal Maternal Anemia With Neurodevelopmental Disorders. JAMA Psychiatry 2019; :1.
16. Lozoff B. Iron deficiency and child development. Food Nutr Bull 2007; 28:S560.
17. Thane-Toe, Thein-Than. The effects of oral iron supplementation on ferritin levels in pregnant Burmese women. Am J Clin Nutr 1982;35:95–9.
18. NIH Office of Dietary Supplements, "Iron: Dietary Sup- plement Fact Sheet," 2007.
19. "Major Pharmaceuticals. Product Catalog," 2011. http://www.majorpharmaceuticals.com/
20. W. Rayburn, R. Aronow, B. DeLancey and M. J. Hogan, "Drug Overdose during Pregnancy: An Overview from a Metropolitan Poison Control Center," Obstetrics & Gy- necology, Vol. 64, No. 5, 1984, pp. 611-614.
21. T. Tran, J. R. Wax, C. Philput, et al., "Intentional Iron Overdose in Pregnancy—Management and Outcome," Journal of Emergency Medicine, Vol. 18, No. 2, 2000, pp. 225-228.
22. Sangkhae V, Nemeth E. Placental iron transport: The mechanism and regulatory circuits. Free Radical Biology and Medicine. 2019 Mar 1;133:254-61.
23. The American College of Obstetricians and Gynecolo- gists, "Planning Your Pregnancy and Birth, Education Pamphlet," 3rd Edition, Washington DC. 2000.

24. J. E. Gray, “Safety (Risk) of Diagnostic Radiology Ex- posures,” In: M. L. Janower and O. W. Linton, Eds., Ra-diation Risk: A Primer, American College of Radiology, Reston (ACR), Reston, 1996, pp. 15-17.
25. G. W. Everson, E. J. Bertaccini and J. O’Leary, “Use of Whole Bowel Irrigation in an Infant Following Iron Over- dose,” American Journal of Emergency Medicine, Vol. 9, No. 4, 1991, pp. 366-369.
26. T. Madiwale and E. Liebelt, “Iron: Not a Benign Thera- peutic Drug,” Current Opinion in Pediatrics, Vol. 8, No. 2, 2006, pp. 174-179.