Anemia and its consequences on human body; A comprehensive overview

Sana Noreen[1]*, Shahid Bashir[1], Sadia Bano[2], Tahira Fatima[2], Affifa Sani[2], Sehar Imran[2], Zainab Saeed[2], Asma Naseer[2], Rafia Ijaaz[2], Khadija Riaz[2], Madiha Khan[2], Maryam Yaseen[2]

[1]University Institute of Diet and Nutritional Sciences, Faculty of Allied Health Sciences, The University of Lahore, **Pakistan.**

[2]University Institute of Diet and Nutritional Sciences, The University of Lahore, **Pakistan.**

Corresponding Author: sananoreen.rizwan@gmail.com

ABSTRACT

Anemia is a pathological condition characterized by a reduction in the mass of red blood cells or the amount of hemoglobin. Anemia affects one-third of the world's population, with iron deficiency accounting for half of the cases. It's a major global public health problem that has an effect on maternal and child mortality, physical fitness, and referral to health-care providers. Underweight children have a greater prevalence of anemia, which can produce long-term developmental outcomes. Particular risk is presented by children 0-5 years, child-bearing mothers and pregnant women. Efforts to avoid anemia should concentrate on improving current supplementary iron and folate programs and on preventing folate and vitamin B12 anemia deficiency. In this review biological mechanism and condition of anemia development has been discussed. A further study is necessary to examine the function of additional nutrient deficits, the contribution of infectious and chronic illnesses in some populations, and the significance of hereditary hemoglobin disorders.

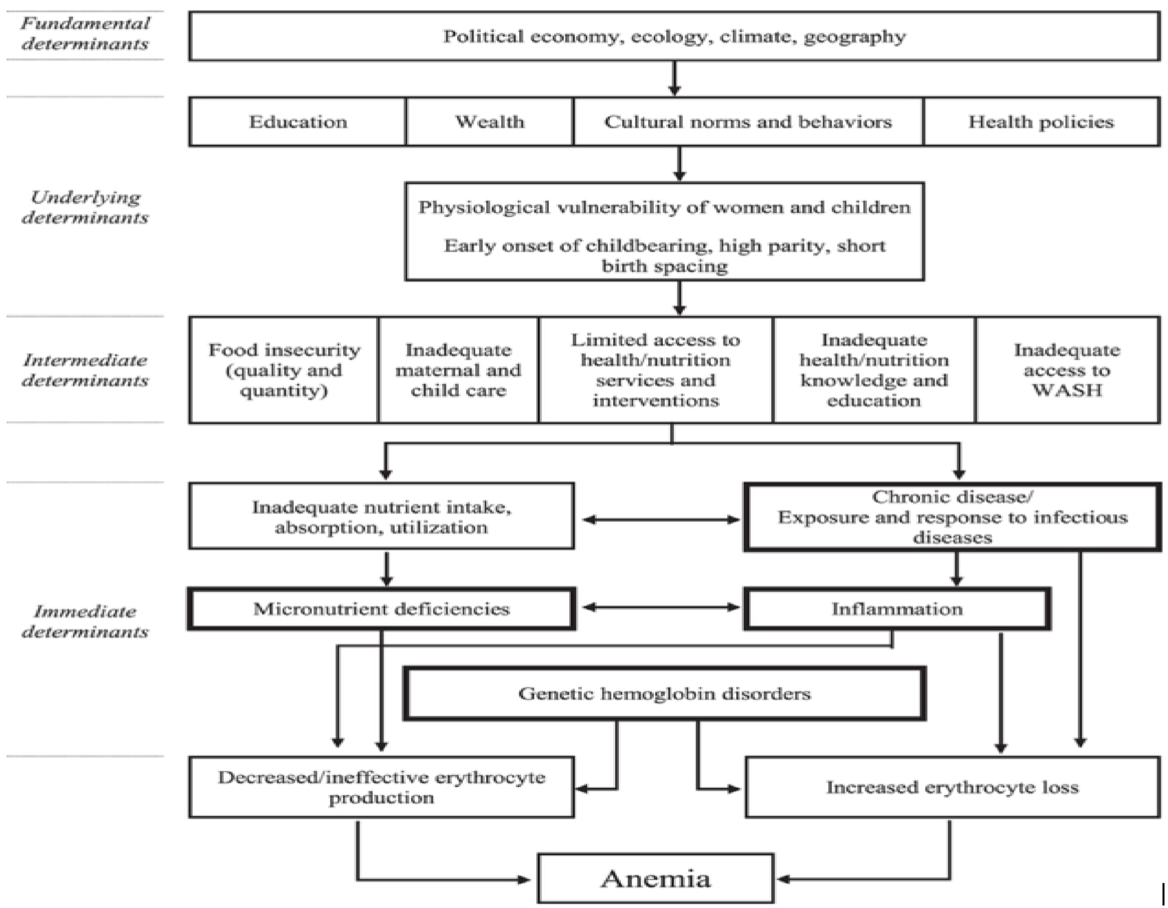
Key Words: Anemia, Inflammation, Hemoglobin, Nutrition, Iron deficiency.

Introduction

Hemoglobin is the red blood cell protein molecule which transports oxygen from the lung to the tissues of the body and returns carbon dioxide from the tissues to the lungs. Hemoglobin consists of four protein molecules bound together (the globulin chains). Two alpha-globulin chains and two beta-globulin chains form the normal adult hemoglobin (Hgb or Hb abbreviated). Anemia is a disease in which the concentration of hemoglobin (Hb) and red blood cells (RBC) are below normal levels, which are inadequate to satisfy the physiological demands of the person affects approximately a third of the world's population. The name comes from ancient Greek: anemia ("lack of blood"), anemia ("not"). Anemia is linked to elevated female and infant morbidity and mortality, adverse birth outcomes in adult employment and reduced cognitive and behavioral growth in infants (Chaparro & Suchdev, 2019). "Anemia is highly common in developing and developed countries and is regarded as a public health concern. It happens at all stages of life, especially in women and children who are pregnant, 1.62 billion people worldwide are anemic". In pre-school children the highest prevalence is 47.4%, in men the lowest prevalence is 12.7%. Anemia is the second leading disease cause in the world and thus one of the most significant public health issues in the world" (WHO, 2018). Anemia has multifactorial causes with complicated interactions among nutritional and other factors, which are a challenge to resolve effectively population determinants of anemia (Antwi-Bafour *et al*., 2016). Anemia has many causes including: "infectious diseases, for instance, malaria, hookworm and shistosomiasis. Micronutrient deficiencies including folate, vitamin B12 and vitamin A. Increased chance of having anemia is also seen in individuals with chronic diseases like kidney diseases, cancer, diabetes and associated conditions". There are different varieties of anemia classifications. Anemia is caused by a variety of red cell defects such as a production defect (AP), a maturation defect (MAM), a hemoglobin synthetic defect (AID) or a genetic defect in the maturation of hemoglobin (THA) or the synthesis of anomalous hemoglobin (HHEA) or thalassemia (Balarajan *et al.*, 2011).

Many studies suggests that fetal/neonatal Iron deficiency discusses long-term risks to brain function. Early iron deficits (ED) not only affect the brain and function, but also have an after-treatment effect. Dopamine synthesis, myelination, composition and function modifications for the long run are part of the path. The brain does not normally function, as it has an iron deficiency. Deficiency in iron Headache, vertigo, delirium, restless leg syndrome are all linked with anemia. Anemia. Anemia is today the main global risk factor for the wellbeing of adolescents and pregnant mothers. Anemia should be diagnosed and treated early in order to achieve a stable generation (Soundarya & Suganthi, 2017).

Conceptual model of anemia etiology



Iron deficiency anemia

Iron deficiency, which affects 2 billion people globally, is the most prevalent nutshell for infants. Worldwide, the rate of iron failure is twice as high as anemia of iron deficiency. (Lanzkowsky *et al.*, 2016). Microorganisms have evolved advanced mechanisms such as the siderophore system to extract iron from extremely low amounts in their atmosphere. Human beings have evolved ways to withhold iron from microorganisms as a primitive defense mechanism. In human ferrokinetics, iron-binding proteins such as transferrin, ferritine, and lactoferrin play a central role. These iron-bound proteins also contribute to a reduction in the supply of iron for microorganisms. They achieve this by reducing the use of iron (Camaschella *et al.,* 2015). Iron deficit can lead to anemia-unrelated symptoms. The most effective iron deficiency test is serum ferritin. Oral iron with vitamin C is best administered once a day (DeLoughery *et al*., 2017).

Types of Anemia

Aplastic Anemia

Aplastic anemia (AA) is a rare bone marrow deficiency condition that is particularly lethal when seriously treated and not properly treated. Aplastic anemia is a seldom condition with a prevalence of around two to three cases annually based on specialized trials, but in Asian populations it may be three times higher. It is a young disease that usually develops during the first 30 years with an average age of about 20 (Shallis *et al.*, 2018). The most prevalence of acquired aplastic anemia is a result of the immune-mediated elimination, either by immune suppressive or haematopoietic stemcell transplant, of hematopoietic stem cells inducing pancytopenia, with empty bone marrow (Young *et al.*, 2008).

Sickle Cell Anemia

Sickle cell anemia is disorder known as sickle cell disease in which there aren't enough healthy red blood cells to carry oxygen throughout the body. In sickle cells RBC's are of sickle shape or looks like crescent moons. "These rigid can stuck in small blood vessels and can stuck or block flow of blood. Signs and symptoms start to appear around 5 months of age". They vary person to person and changes over time. Sickle cells break apart easily and then die leaving too few red blood cells. "The life span of RBC's is 120 days. But sickle cells usually die in 10 to 20 days, leaving a shortage of red blood cells (anemia)" (Adams *et al.,* 1998). It is caused by a gene mutation that instructs the body to produce the iron-rich compound that gives blood its red color and allows red blood cells to transport oxygen from the lungs to the rest of the body (hemoglobin). "Pain occurs as sickle-shaped red blood cells obstruct blood flow to the chest, belly, and joints through tiny blood vessels, develop ulcers, as well as damage to the spleen, joints, and bones, as a result of a chronic pain crisis". If the condition persists, a hospital stay may be required. Hand and foot swelling, viruses on a regular basis, delayed growth and puberty, pale skin, confusion, headache, fatigue (Sabarense *et al.*, 2015).

Hemolytic Anemia

With an MCV of 80 to 100 fL, hemolytic anemia is classified as normocytic anemia. It is a type of low hemoglobin caused by red blood cell loss, increased hemoglobin catabolism, decreased hemoglobin levels, and increased efforts by the bone marrow to regenerate products. It may be either intrinsic or extrinsic in nature. Infections, cancer, cancers, and drug side effects are examples of extrinsic causes. Intrinsic factors: Red blood cells don't work well, and their hemoglobin is irregular. It contains sickle cell anemia and thalassemia. Often known as erythrocytosis. Hemolytic anemia will strike someone at any age (Rai *et al*., 2020). Hemolytic anemia can damage various organ systems in the body. In hemolytic cases, ischemia and thrombotic complications are also possible. Patients can feel muscle pain and fatigue when muscles are deprived of blood and oxygen, and extra iron from hemolysis may cause kidney failure or complications (Nemeth & Ganz, 2014). Fever, intolerance to physical activity, chills, a larger liver or spleen, confusion, heart palpitations, jaundice, back pain, headache, shock, arrhythmias (irregular heart rhythms), and cardiomyopathy (in which the heart expands larger than normal) are all symptoms of severe hemolytic anemia. Treatment includes blood transfusions, corticosteroids, and other medicines (Cappellini *et al*., 2020).

Complications due to Anemia

Complications during Pregnancy

Anemia is normal in breastfeeding, with rates ranging from 5.4 percent to more than 80 percent in developing countries. For expansion of the maternal blood volume, placental development, and fetal growth, iron requirements rise sharply during pregnancy. A total of 1,040 to 1,240 mg of iron is expected to be needed (Beard & Durward, 2012). Anemia's severity is linked to an elevated risk of LBW and prematurity. Anemia due to iron deficiency accounts for 75% of all anemia in pregnancy. IDA is linked to an elevated risk of preterm labor, low neonatal weight, and perinatal risks in pregnant mothers. Owing to a decreased threshold for acute blood loss during gestation and an elevated risk of infections, severe IDA is linked to an increased risk of infant and maternal mortality (Beard & Durward, 2012).

Maternal Mortality and Morbidity in Anemia

Anemia, and its most common symptom, iron deficiency (ID), is a common cause of morbidity in both developed and developing countries. “Women with hemoglobin levels below 8 gm/dl have a higher risk of maternal morbidity. Additional causes, such as social status, medical treatment, and dietary status, can be linked to maternal morbidity (Breymann, 2015). When maternal hemoglobin levels dip below 5.0 g/dl, maternal mortality rates skyrocket. Women with moderate anemia are more likely to die from antepartum and postpartum hemorrhage, pregnancy-induced hypertension, and sepsis. The severity of the iron deficiency anemia affects maternal mortality as well. An increased risk of cardiovascular disease, a high risk of hemorrhagic shock, and higher rates of infection and delayed wound healing during the puerperium are among the causes” (Breymann, 2015).

Child Growth defects

Anemia in children is characterized as a hemoglobin (Hb) concentration below the World Health Organization's cutoff thresholds. “Iron deficiency anemia (IDA) is the most common cause of anemia in children aged 6–59 months, 11.5% in children aged 5–11 years, and 12 g/dl in older children. (Ashraf *et al.*, 2017). Inadequate iron consumption during the quickly developing years of infancy and childhood is the most frequent cause of iron deficiency anemia. During infancy, growth is particularly rapid. Iron reserves available at birth will be exhausted by 6 months in a full-term baby and by 34 months in a premature infant if no iron is present in the diet or if blood loss happens” (Lanzkowsky, 2016). Anemia has been associated with growth retardation including stunting and being underweight. Complications such as growth and pubertal delay are normal. Defective IGF-I secretion is one of the mechanisms of defective development in children with IDA. (Ashraf *et al*., 2017). ID also has a detrimental effect on the mother-child relationship and the neurological growth of children, with effects lasting up to ten years despite iron replacement (Camaschella, 2015).

Complications in Adolescence

Adolescents are people aged 10 to 19 years old, according to the World Health Organization. This age group accounts for roughly 20% of the global population, and it is during this time that people transition from dependent childhood to independent adulthood (Teji *et al.*, 2016). Human babies may have chronic symptoms of early life iron deficiency that continue into adulthood, causing cognitive dysfunction in the elderly and restless leg syndrome (Cappellini *et al.*, 2020). On chronically anemic teenagers, adolescence is a susceptible time in the human life cycle for nutritional anemia. According to a survey, the most prevalent form of anemia in adolescents was megaloblastic anemia (42.5%), with iron deficiency accounting for 15% of cases. Deficiency in folate, vitamin B12 and iron are all normal in anemic teens. Vegetarianism was shown to be linked to extreme anemia. Menarche was also interrelated to an increased risk of anemia, according to researchers who found that high menstrual blood loss was linked to an increased risk of anemia. Iron, folic acid and vitamin B12 supplementation should be provided in the community (Cappellini *et al.*, 2020).

Lowered Cellular Immunity and Increased Morbidity

Iron is required for the immune system's normal growth. A healthy iron homeostasis is crucial in deciding infection tolerance and outcome. Its absence impairs the immune system's ability to respond appropriately because it is needed for immune cell proliferation and the production of complex responses to infection (Das *et al.*, 2014). Iron is a critical component for the immune system's normal growth, according to research from the last few decades. Iron is required for immune cell proliferation, especially lymphocyte proliferation, which is linked to the generation of a specific response to infection. Iron is needed for monocyte/macrophage separation, and macrophages need iron as a cofactor to carry out essential antimicrobial effector mechanisms, such as the nicotinamide adenine dinucleotide phosphate hydrogen-dependent oxidative blast (Hassan *et al.*, 2016). Anemia is the most common nutritional condition in the world, with iron deficiency being the most common cause (ID). ID is particularly dangerous to children and women of reproductive age. Hemoglobin levels below 10 gm/dl hinder cell-mediated immune responses, resulting in bacterial growth in leucocytes in young children. Cause hemodynamic Instability, reduced Immune Response which can make older adults more vulnerable to infections (Cappellini *et al.*, 2020).

Anemia and Chronic kidney disease

Renal function will not be harmed by mild to severe anemia because blood is drawn to the kidneys from peripheral tissues. The kidneys are also one of the organs that helps the bone marrow make RBCs by increasing erythropoietin secretion. The synthesis of this hormone is reduced in people with chronic (long-term) kidney disease, which lowers RBC production (Abbaspour *et al.,* 2014). As a result, kidney function is compromised, resulting in anemia. Since erythropoietin deficiency is the most common cause of anemia in chronic renal failure. With declining hemoglobin levels, there is a cumulative rise in the risk of pre-dialysis death or the occurrence of end-stage renal disease in predialysis patients (around 2- to 3-fold for hemoglobin values <120 vs >130 g L^{-1}). (Cappellini *et al.*, 2020).

Anemia and Cardiovascular Disease

Cardio-renal anemia syndrome is characterized by anemia which is linked to a two-fold increased risk of cardiovascular hospitalization. Lack of iron Fatigue, tachycardia, cardiac murmer, and angina are also symptoms of anemia, as well as decreased physical function and quality of life (Cappellini *et al.,* 2020). Anemia was observed in 17 percent of heart failure patients in a survey, with chronic disease anemia accounting for the majority of the cases (58 percent). In this significant cohort of individuals with heart disease, those with anemia have a 10% higher 5-year mortality risk (Abid *et al*., 2019). As Hb falls below a certain threshold, compensatory processes fail, lactic acid levels increase, and cardiac failure may occur. Congestive heart disease patients are anemic on average in 40% of cases. “Hypoxia caused by anemia, regardless of the cause, causes peripheral vasodilation, a drop in blood pressure, and activation of the sympathetic and renin angiotensin aldosterone systems (RAAS) to keep blood pressure in check. Increased sympathetic activation raises heart rate and stroke volume, which, when combined with an activated RAAS, will result in renal ischemia, fluid accumulation, and increased plasma volume”. Also in healthy hearts, the elevated cardiac burden caused by both of these pathways will contribute to CHF. TNFa and other cytokines are produced by compromised myocardium and can cause additional damage to the heart and kidneys. This, in fact, will worsen anemia (Silverberg *et al.*, 2001).

Anemia and Gastrointestinal Tract (GIT)

Anemia is associated with gastrointestinal disturbances. Any of them, including duodenal ulcer, gastrointestinal tract carcinoma or glossitis, and atrophy of the tongue papillae in pernicious anemia, may be symptoms of the underlying condition. In anemic patients, indigestion and irregular bowel movements have also been identified (Percy *et al.*, 2017).

Chronic Inflammatory disorders and Anemia

Inflammatory bowel diseases (IBD), include “Crohn's disease” and “ulcerative colitis”, are chronic inflammatory disorders. Anemia is a frequent symptom of inflammatory bowel disease (IBD). In IBD, persistent anemia is normal. Anemia affects 5%–71% of IBD patients, according to reports. Anemia is more frequent in children than in adults with IBD (Goodhand *et al.*, 2012). According to a new meta-analysis of European studies, Crohn's disease (CD) has a prevalence of 27% and Ulcerative colitis has a prevalence of 21%. (UC). Crohn's disease (CD) often progresses from an inflammatory state to a more complex state of stenoses or fistulae. Ulcerative colitis (UC) can spread over time, raising the likelihood of a colonoscopy or cancer. Persistent or chronic anemia in patients with IBD is linked to more aggressive or debilitating illness, according to a prospective study of 410 patients. The most prominent extraintestinal manifestation of inflammatory bowel disease is iron deficiency anemia, which can have a negative impact on one's quality of life (Cappellini *et al.*, 2020).

Anemia and Genitourinary Tract

Symptoms of the genitourinary tract are common in anemia patients, and they can be caused in part by a reduction in sexual hormone secretion. Amenorrhea, menorrhagia, and erratic menstrual cycles are among the more frequent symptoms (Percy *et al.*, 2017).

Anemia and Altered Brain Function

Late fetal/early neonatal life, toddlerhood, and puberty are three peak ages for iron deficiency in early life, all of which are associated with lower brain development during the duration of ID. According to several findings, fetal/neonatal iron deficiency is associated with long-term risks to brain development. (Cappellini *et al.*, 2020). Early iron deficiency (ID) has long-term effects on brain and behavioral function, not just during the ID phase. Long-term changes in dopamine synthesis, myelination, and hippocampal development and function are among the pathways. When the brain is iron deficient, it does not function properly. Headache, vertigo, syncope, delirium, and restless leg syndrome are all symptoms of anemia. In iron deficiency, restless leg syndrome has been characterized as an uncontrollable movement of the legs. According to a meta-analysis of five tests, a 10 g/L rise in hemoglobin was linked to a 173 (95%) increase in IQ marks (Teji *et al.*, 2016). However, whether or not impaired cognitive performance in iron-deficient children is exacerbated by other causes leads to poor cognitive functions remains to be seen (Balarajan *et al.*, 2014). Iron is needed for normal energy metabolism, neurotransmitter synthesis, and myelination in neurons and glia. "Acute neurobehavioral effects of neonatal ID include altered temperament and child-mother interaction, slower neural conduction velocity, a higher prevalence of abnormal neurologic reflexes, and poorer discrimination memory, whereas long-term effects are related to dopamine and monoamine or neurotransmitter metabolism in general." (Yohannes & Ershler, 2011).

Preventive measures of anemia

Other types of anemia, such as inherited anemia, cannot be prevented. However, consuming a healthy diet can help avoid anemia caused by iron deficiency, vitamin B12 deficiency, and vitamin B9 deficiency. This involves consuming a diet rich in foods rich in iron and these vitamins, as well as vitamin C-rich foods to aid absorption. Make sure you're getting enough water. Anemia can occur for a variety of reasons, but one of the most common is inadequate diet (WHO, 2017). Other micronutrients can be deficient in insufficient and unbalanced diets, contributing to micronutrient shortages and the development of anemia. To combat this, a variety of dietary-improvement-focused interventions have been applied at the community level or are specifically aimed at disadvantaged populations such as babies, small children, and pregnant women. It includes food-based methods for reducing micronutrient deprivation and increasing micronutrient consumption, such as supplementation, food fortification, and improving the diversity and consistency of food (Zimmermann *et al.*, 2007).

Dietary Strategies

A nutritious, well-balanced diet can help avoid deficiencies. Strong sources of iron include liver, red meat, beans, lentils, tofu, fish, dried fruit, and dark leafy greens. Vitamin B12 and folic acid are both needed for RBC processing. These are abundant in dairy products, milk, bananas, and spinach. Minerals, vitamin B12, and folic acid are also present in fortified breads, cereals, and pastas. Vitamin C is abundant in citrus fruits and other types of food, which is also essential (Maldonado, 2013).

Supplementation

Daily or occasional oral iron, nutrient, or mineral supplementation alone or in combination (especially vitamin B12, folate, vitamin A, or pro vitamin A, but also vitamin C, vitamin E, zinc, and other minerals). Supplementation during breastfeeding has been linked to the prevention of maternal anemia in people who live in areas where vitamin A deficiency is prevalent. For most diets, meeting the high physiological demand for iron during pregnancy is challenging. During breastfeeding, a woman requires about 2–2.8 mg of iron every day. "During breastfeeding, iron needs range from 450 to 1,150 mg, with a median of 790 mg. Folic acid supplements are more effective than dietary folate at raising serum levels. Adults should take 400 mcg/day, pregnant women 600 mcg/day, and breast-feeding mothers 500 mcg/day. In all cases, intake is limited to 1000 mcg/day" (Sabarense *et al.*, 2015).

Food Fortification with Iron and Vitamin B12

Iron fortification involves the addition of iron, usually with folic acid. The presence of iron, normally in the form of folic acid, is known as iron fortification. Thus, iron fortification of foods has emerged as a potential strategy for avoiding iron deficiency anemia during breastfeeding. Iron was fortified into a number of foods, including cereal flour (maize or wheat), salt, beverage, milk, and sugar, pasta, rice, and fish sauce, and used effectively as nutritional supplements to avoid anemia (Girard & Olude, 2012). Even though vitamin B12 does not exist naturally in plant foods, fortified foods should be used in these situations (Sabarense *et al.*, 2015). The daily recommended intake of "vitamin B12 in adults is 2.4 mcg/day, and 2.6 mcg/day and 2.8 mcg/day in pregnant and breast feeding women." (Soundarya & Suganthi, 2017).

Conclusion

Anemia is the biggest nutrition problem occurring these days. Iron deficiency anemia is most common type affecting children and pregnant women. Another type (genetic) Sickle cell anemia is caused due to crescent shape red blood cells. Hemolytic anemia is low hemoglobin due to the destruction of red blood cells. Common symptoms of anemia includes Dizziness, Weakness, Tiredness, pale skin pallor, irritability, anorexia, and pica. On average 80% women during pregnancy are anemic that increases the chances of death of mother or fetus, or result in early deaths or multiple post birth disorders like birth defects, impaired thermoregulation, Lowered Cellular Immunity and Increased Morbidity and Compromised development in infants and Young children. Chronic anemia cause organ damage effecting kidneys, heart, inflammation in gastrointestinal tract and impaired brain functions. Inherited anemia can't be treated. Iron levels can be maintained and regulated by proper dietary practices eating varieties of foods including fruits, vegetables, pulses and legumes high protein diet and iron rich diet and fortified food products. Micro nutrient supplementations are recommended according to need and nutritional status.

References:

Chaparro, C.M. and Suchdev, P.S., 2019. Anemia epidemiology, pathophysiology, and etiology in low-and middle-income countries. *Annals of the New York Academy of Sciences*, *1450*(1), p.15.

Antwi-Bafour, S., Hammond, S., Adjei, J.K., Kyeremeh, R., Martin-Odoom, A. and Ekem, I., 2016. A case–control study of prevalence of anemia among patients with type 2 diabetes. *Journal of medical case reports*, *10*(1), pp.1-8.

Balarajan, Y., Ramakrishnan, U., Özaltin, E., Shankar, A.H. and Subramanian, S.V., 2011. Anaemia in low-income and middle-income countries. *The lancet*, *378*(9809), pp.2123-2135.

Soundarya, N. and Suganthi, P., 2017. A review on anaemia–types, causes, symptoms and their treatments. *Journal of science and technology investigation*, *1*(1).

Girard, A.W. and Olude, O., 2012. Nutrition education and counselling provided during pregnancy: effects on maternal, neonatal and child health outcomes. *Paediatric and perinatal epidemiology*, *26*, pp.191-204.

Adams, R.J., McKie, V.C., Hsu, L., Files, B., Vichinsky, E., Pegelow, C., Abboud, M., Gallagher, D., Kutlar, A., Nichols, F.T. and Bonds, D.R., 1998. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. *New England Journal of Medicine*, *339*(1), pp.5-11.

Sabarense, A.P., Lima, G.O., Silva, L.M. and Viana, M.B., 2015. Characterization of mortality in children with sickle cell disease diagnosed through the Newborn Screening

Program. *Jornal de pediatria*, *91*(3), pp.242-247.

Rai, M., Ali, M.U. and Geller, C., 2020. Hemolytic Anemia: Sneaky Cause, Leaky Valve. *Cureus*, *12*(5).

Lanzkowsky, P., Lipton, J.M. and Fish, J.D. eds., 2016. *Lanzkowsky's manual of pediatric hematology and oncology*. Academic press.

Camaschella, C., 2015. Iron-deficiency anemia. *New England journal of medicine*, *372*(19), pp.1832-1843.

DeLoughery, T.G., 2017. Iron deficiency anemia. *Medical Clinics*, *101*(2), pp.319-332.

Nemeth, E. and Ganz, T., 2014. Anemia of inflammation. *Hematology/Oncology Clinics*, *28*(4), pp.671-681.

Shallis, R.M., Ahmad, R. and Zeidan, A.M., 2018. Aplastic anemia: etiology, molecular pathogenesis, and emerging concepts. *European journal of haematology*, *101*(6), pp.711-720.

Young, N.S., Scheinberg, P. and Calado, R.T., 2008. Aplastic anemia. *Current opinion in hematology*, *15*(3), p.162.

Cappellini, M.D., Musallam, K.M. and Taher, A.T., 2020. Iron deficiency anaemia revisited. *Journal of internal medicine*, *287*(2), pp.153-170.

Abid, S.A., Gravenstein, S. and Nanda, A., 2019. Anemia in the long-term care setting. *Clinics in geriatric medicine*, *35*(3), pp.381-389.

Hassan, T.H., Badr, M.A., Karam, N.A., Zkaria, M., El Saadany, H.F., Rahman, D.M.A., Shahbah, D.A., Al Morshedy, S.M., Fathy, M., Esh, A.M.H. and Selim, A.M., 2016. Impact of iron deficiency anemia on the function of the immune system in children. *Medicine*, *95*(47).

Abbaspour, N., Hurrell, R. and Kelishadi, R., 2014. Review on iron and its importance for human health. *Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences*, *19*(2), p.164.

Breymann, C., 2015, October. Iron deficiency anemia in pregnancy. In *Seminars in hematology* (Vol. 52, No. 4, pp. 339-347). WB Saunders.

Yohannes, A.M. and Ershler, W.B., 2011. Anemia in COPD: a systematic review of the prevalence, quality of life, and mortality. *Respiratory care*, *56*(5), pp.644-652.

Beard, J.L. and Durward, C., 2012. The liabilities of iron deficiency. In *Iron physiology and pathophysiology in humans* (pp. 283-302). Humana Press.

Teji, K., Dessie, Y., Assebe, T. and Abdo, M., 2016. Anaemia and nutritional status of adolescent girls in Babile District, Eastern Ethiopia. *Pan African Medical Journal*, *24*(1).

Goodhand, J.R., Kamperidis, N., Rao, A., Laskaratos, F., McDermott, A., Wahed, M., Naik, S., Croft, N.M., Lindsay, J.O., Sanderson, I.R. and Rampton, D.S., 2012. Prevalence and management of anemia in children, adolescents, and adults with inflammatory bowel disease. *Inflammatory bowel diseases*, *18*(3), pp.513-519.

Ashraf, T.S., De Sanctis, V., Yassin, M. and Adel, A., 2017. Growth and growth hormone-insulin like growth factor-I (GH-IGF-I) axis in chronic anemias. *Acta Bio Medica: Atenei Parmensis*, *88*(1), p.101.

Das, I., Saha, K., Mukhopadhyay, D., Roy, S., Raychaudhuri, G., Chatterjee, M. and Mitra, P.K., 2014. Impact of iron deficiency anemia on cell-mediated and humoral immunity in children: A case control study. *Journal of natural science, biology, and medicine*, *5*(1), p.158.

Silverberg, D.S., Iaina, A., Wexler, D. and Blum, M., 2001. The pathological consequences of anaemia. *Clinical & Laboratory Haematology*, *23*(1), pp.1-6.

Percy, L., Mansour, D. and Fraser, I., 2017. Iron deficiency and iron deficiency anaemia in women. *Best practice & research Clinical obstetrics & gynaecology*, *40*, pp.55-67.

Maldonado, J.R., 2013. Neuropathogenesis of delirium: review of current etiologic theories and common pathways. *The American Journal of Geriatric Psychiatry*, *21*(12), pp.1190-1222.

Zimmermann, M.B. and Hurrell, R.F., 2007. Nutritional iron deficiency. *The lancet*, *370*(9586), pp.511-520.

Anaemias, W.N., 2017. Tools for effective prevention and control. *Geneva: World Health Ognanization*.

World Health Organization, 2011. *Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity* (No. WHO/NMH/NHD/MNM/11.1). World Health Organization.

Latham, M.C., Ash, D.M., Makola, D., Tatala, S.R., Ndossi, G.D. and Mehansho, H., 2003. Efficacy trials of a micronutrient dietary supplement in schoolchildren and pregnant women in Tanzania. *Food and nutrition bulletin*, *24*(4), pp.S120-S128.