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Review Article

Impact of Anemia in Development of Infants: A Review

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Abstract

Anemia is a global public health issue that affects roughly one-third of the world's population. Anemia causes both short-term and long-term devastating complications in infants and children. Despite the fact that anaemia is a major public health concern, newborns, particularly in developing countries, are frequently overlooked and undiagnosed. It is a condition where the amount of red blood cells or the amount of haemoglobin they contain is below normal. There will be a reduced ability of the blood to transfer oxygen to the body's tissues if you have insufficient or atypical red blood cells, insufficient haemoglobin, or both. Nutritional deficiencies, particularly iron deficiency, are the most frequent causes of anaemia, though deficiencies in folate, vitamins B12, and A are also significant contributors.

The important public health issue of anaemia disproportionately affects young children. According to WHO statistics, anaemia affects 40% of pregnant women and 42% of children under the age of five worldwide. Iron deficiency is common among infants and young children, particularly in developing countries.

Despite iron repletion, animal models show that iron deficiency during the brain growth spurt alters metabolism and neurotransmission, myelination, and gene and protein profiles. In humans, there is compelling evidence that 6- 24-month-old infants with iron deficiency anaemia have poorer short and long term cognitive, motor, social-emotional, and neurophysiologic development.

In contrast to the inconsistent developmental effects of iron therapy for iron deficient infants, recent large, randomized trials of iron supplementation in developing countries consistently show iron benefits, particularly on motor development and social emotional behaviour. These findings suggest that iron can be used to prevent and or reverse negative effects earlier in development or before iron deficiency occurs.

Keywords: Anemia; Red Blood Cells; Hemoglobin

Introduction

Anemia is derived from the Greek word anemia, which indicates a lack of blood. Anemia is a disorder characterized by a lack of red blood cells or hemoglobin, which results in a decrease in the oxygen-carrying capability of blood to various organs in the human body [1]. Anemia can also occur when the rate of erythrocyte loss exceeds the rate of formation [2].

Anemia in newborn babies can range from asymptomatic to a life-threatening event [3].

It causes a delay in brain maturation, tissue hypoxia, and stunted growth if left untreated. Its prevalence ranges from 23-66% in Sub-Saharan Africa. However, there is little information available in Ethiopia about the prevalence and risk factors for newborn anemia [4].

Neonatal anemia, defined as a hemoglobin (Hb) or hematocrit (Hct) concentration that is more than two standard deviations below the mean for postnatal age, is a significant problem in neonatal intensive care units (NICUs). Newborns are one of the most transfused groups, with 90% of extremely low birth weight infants receiving at least one RBC transfusion during their NICU stay [5]. A low Hb level at birth has recently emerged as a risk factor for mortality and the likelihood of receiving a blood transfusion in preterm infants born at 32 weeks of gestation, regardless of mode of delivery or time of umbilical cord clamping [6].

Hematocrit (Hct) drops down after birth due to physiological factors [1,7]. Despite higher breastfeeding rates, public health improvements, and the creation of iron-fortified foods, the prevalence of anaemia and iron deficiency anaemia remains high in late

infancy and early childhood [8,9]. Iron deficiency anemia is still a major public health concern that necessitates screening of pediatric patients [10,11]. More precise testing methods are currently being investigated [12]. Iron deficiency anemia may be prevented through dietary interventions during rapid periods of growth, as well as supplementation for at-risk patients [13].

Long term anemia has the potential to affect both brain growth and other chronic disease components in both premature and term infants [14]. A significant number of physiologic changes in erythropoiesis occur at birth, leading to a transitory anemia known as physiologic anemia of childhood in the term infant. Premature infants may have exaggerated physiologic anemia due to a variety of endogenous and exogenous factors. The causes of neonatal anemia can be divided into three major categories: blood loss, decreased production, and increased erythrocyte destruction [1,15]. Hemoglobin's primary function is to transport oxygen to tissues and return carbon dioxide to the lungs for elimination from the body. Anemia can be caused by any condition that causes a lack of functional hemoglobin or a decrease in red blood cell (RBC) mass. As a result, the pathophysiology of anemia is diverse and frequently multi factorial. Genetic mutations in hemoglobin genes, acute and chronic blood loss, insufficient nutritional intake, altered red blood cell morphology leading to shortened RBC life span, infectious processes, or changes in iron and RBC metabolism secondary to chronic inflammation are all possible causes. A lack of iron—the building block of each hemoglobin molecule—is a common symptom of many conditions that cause anemia [16].

Characteristics of neonatal erythrocytes

- The life span of a red blood cell (RBC) at birth is shorter than that of an adult: 60-70 days (preterm 35-50 days) compared to 90-120 in adults, most likely due to increased RBC rigidity.
- RBCs at birth are more resistant to osmotic lysis, have a larger mean corpuscular volume and lower mean corpuscular hemoglobin concentration, and are more susceptible to oxidant-induced injury, owing to a lack of phosphofructokinase activity [14].
- Peripheral blood smear: high frequency of RBC dysmorphology in term neonates (only 43% have disc appearance compared to 78% in adults and 14% are spherocytes and poikilocytes compared to 3% in adults) and even more in preterm neonates.
- In the first few weeks after birth, hemoglobin switches from HbF to HbA.
- Due to a decrease in EPO in the plasma, the rate of hemoglobin synthesis and RBC production drops dramatically during the first few days after delivery.
- Iron homeostasis in newborns with low hepcidin levels differs [14].

Risk factors [17]

- Babies born prematurely or with low birth weight.
- Infants fed cow's milk before the age of 12 months.
- Babies who were fed non-iron-fortified formula.
- Children between the ages of one and five who drink more than 25 ounces of cow, goat, or soy milk per day.
- Children with specific health requirements, such as chronic infections or dietary restrictions.
- Maternal anemia, diabetes, a restricted diet (for example, veganism), or a low socioeconomic status.
- Infections caused by hookworm or schistosomiasis, for example, necessitate a needs assessment for migrants from developing countries [17].

Classification of anemia

According to Figure 2, anaemia is categorised according to the shape of red cells, red cell indices, and haemoglobin concentration. The three types of anaemia—hypochromic microcytic, normochromic normocytic, and macrocytic anaemia—are illustrated in figure 2.

Based on the RBC shape, it is further divided into the anaemias Iron Deficiency Anemia (IDA), Sickle Cell Anemia (SCA), thalassemia, Hereditary Spherocytosis (HS), Hereditary Elliptocytosis (HE), aplastic anemia, and Hemolytic Anemia (HA). The kinds of normal and abnormal red blood cells are depicted in Figure 3 based on their morphology. The classification of anaemia can also be done using clinical indicators like RBC count, RBC markers like mean corpuscular or cell volume (MCV in femto litre), mean cellular haemoglobin concentration (MCHC), mean cell haemoglobin content (MCH in picograms), and red cell distribution width. (RDW). These variables are crucial for the identification and categorization of anaemia. If RBC indices are abnormal, haematologists typically investigate peripheral blood smears (represented in figure 1). Table 1 illustrates the morphological categorization of anaemia based on the clinical diagnosis [18].

Figure 1: Microscopic view of blood smear [18].

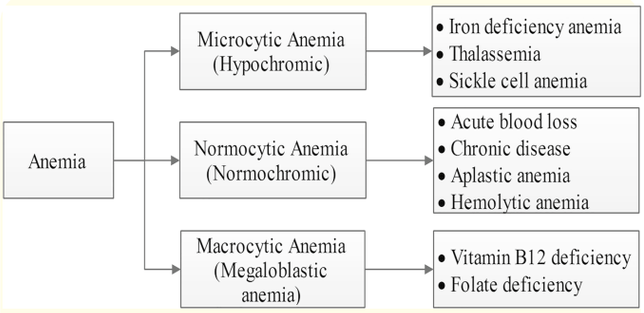

Figure 2: Classification of anaemia [18].

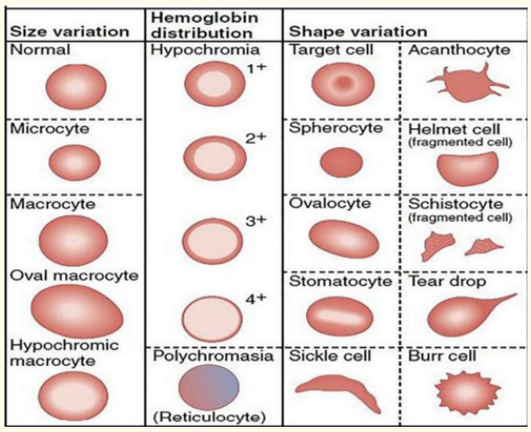

Figure 3: Abnormal and normal RBC's [18].

Table 1: Classification of anaemia based on clinical parameters [18].

Anemia Type	MCV fL	MCH pg	MCHc %
Macrocytic anemia	> 100	> 32	32–35
Normocytic anemia	80–100	27–32	32–35
Microcytic anemia	< 80	< 27	< 32

Iron deficiency anemia (IDA)

Iron is an essential micro nutrient for human growth and development at all stages of life. Its deficiency is the primary cause of anemia, which is a major worldwide health issue and a burden for impoverished nations. Iron Deficiency Anemia (IDA) is the most frequent nutritional deficiency illness that has been impacting the health of millions of individuals worldwide for decades. Iron deficiency is the major cause of many metabolic illnesses that cause disability and mortality in vulnerable people all over the world. Although IDA is most common in children and women, adult males from both developed and developing countries are prone to iron deficiency due to their socioeconomic level and health condition [19].

IDA affected 1.62 billion individuals, or around 24.8 percent of the world's population.

Preschoolers (42.6%) had the greatest frequency of IDA in 2011, followed by pregnant women (38.2%) and non-pregnant women (29.0%).

According to the World Health Organization, iron deficiency in the food accounts for 50% of anemia cases (WHO 2008), while additional causes of anemia include a lack of pyroxidine, folate, cobalamin, and proteins in the diet (Premkumar, Ramanan, and Thanka 2018). Anemia is also linked to chronic inflammation, parasite infections, and a lack of personal cleanliness and proper sanitation habit. Current research investigations have also revealed that the prevalence of anemia differs by country or location [20]. Iron, proteins, b-complex vitamins, ascorbic acid, copper, and zinc-rich diets aid enhance iron storage, but phytate, fibre, oxalate, and tannins inhibit iron absorption [2].

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Major causes of Iron Deficiency Anemia (IDA)

- Blood Loss
- The Maternal–Fetal Bridge of Iron Deficiency
- Malaria
- Hookworm [20]

Reduction strategies

Iron fortification, dietary variety, supplementing techniques, and nutritional education are all possibilities for reducing anemia. There is a need for better public awareness of the difficulties connected with anemia, as well as nutrition education and dietary supplementation of hematinic foods to boost iron reserves. This section discusses some of the anti-IDA techniques [2].

Iron supplementation

Iron fortification is the most effective and widely used method of dealing with iron deficiency in underdeveloped nations. This section examines the many forms of iron fortificants, their GRAS status, and the techniques of food fortification and bio fortification [20].

Sickle cell anemia (SCA)

Sickle cell anemia (SCA) has been recognized in Africa for generations; however, it was not formally described in the western literature until November 1910, when Herrick reported a case of anemia in a dental student from Grenada that was associated with "peculiar elongated and sickle-shaped red blood corpuscles" on microscopy. When Pauling identified SCA as the first "molecular illness" in 1949, he attributed its cause to the presence of an aberrant hemoglobin, hemoglobin S (HbS).

Ingram (100) revealed in 1957 that HbS was induced by a single amino acid substitution (glutamic acid converted to valine) at position 6 of the hemoglobin -globin chain, and Goldstein demonstrated in 1963 that this amino acid substitution was caused by a single base change (A>T) at codon 6 [22,23].

Pathophysiology

The underlying event that underpins the many pathologic repercussions of SCA is the polymerization of HbS under low oxygen tension circumstances [24]. HbS polymerization changes the shape and function of erythrocytes, triggering a chain reaction that affects a wide variety of tissues and has far-reaching clinical and pathological effects. Our comprehension of these processes has lately been boosted by innovative tools, the use of mouse models being particularly significant [22,23].

Preventive actions

Infants with SCA have early loss of filtrative splenic function as a result of vascular congestion, intra parenchymal sickling, and hypoxic injury to the spleen, making them vulnerable to acute life-threatening infections. This risk increases throughout life, but is most pronounced in the first five years, when the incidence of bacteremia is highest [23].

Thalassemia

Beta-thalassemia's are a group of hereditary blood disorders characterized by errors in the synthesis of hemoglobin's beta chains, which result in a wide range of phenotypes ranging from severe anemia to clinically asymptomatic individuals [25]. The term thalassemia comes from the Greek words thalassa (sea) and haima (disease) (blood). Beta-thalassemia syndromes are a group of hereditary blood disorders characterized by reduced or absent beta globin chain synthesis, resulting in low hemoglobin (Hb) levels in red blood cells (RBC), decreased RBC production, and anemia [26,27].

Types of Thalassemia

- Thalassemia major
- Thalassemia intermedia
- Thalassemia minor

Major beta-thalassemia

Thalassemia major manifests clinically between the ages of 6 and 24 months. Affected newborns are unable to thri and become more pale. Feeding difficulties, diarrhea, irritability, recurring spells of fever, and increasing abdominal enlargement due to spleen and liver enlargement may develop. In some developing countries, where patients are untreated or poorly transfused due to a lack of resources, the clinical picture of thalassemia major is characterized by growth retardation, pallor, jaundice, poor musculature, genu valgum, hepato splenomegaly, leg ulcers, the development of masses from extra medullary hematopoiesis, and skeletal changes caused by bone marrow expansion. Deformities in the long bones of the legs and typical craniofacial alterations are examples of skeletal modifications [25,26].

Beta-thalassemia intermedia

Patients at the severe end of the clinical spectrum present between the ages of 2 and 6 years, and while they are capable of surviving without frequent blood transfusions, their growth and development are slowed. At the opposite end of the range, patients with only slight anemia are entirely asymptomatic until adulthood [25,27].

Minor beta-thalassemia

Carriers of thalassemia minor are normally asymptomatic, however they may experience moderate anemia. When both parents are carriers, there is a 25% chance of having children with homozygous thalassemia during each pregnancy [25,26].

Transplantation of umbilical cord blood

The possible advantages of umbilical cord blood (UCB) therapy include a lower chance of virus contamination from a transplant, a lower incidence of acute and chronic GVHD (**Graft versus host disease**) , and ease of access. The small size or quantity of stem cells in the UBC collection relative to the amount necessary for engraftment are likely the major causes of UCB transplantation failure; hence, this surgery is employed mostly in juvenile patients [25].

Aplastic anemia

Aplastic anemia (AA) is a potentially fatal hematopoietic stem cell (HSC) condition with an estimated annual incidence of 2-3 per million [28]. The incidence is tri phasic, with the first peak happening in patients aged 2-5 years, the second peak occurring in patients aged 20-25 years, and the third peak appearing in patients aged.60 years. Pancytopenia with hypo cellular marrow in the absence of aberrant infiltration or marrow fibrosis characterizes it [24]. Exclusion of clonal illnesses, such as myelo dysplastic syndrome (MDS), hypo cellular myeloid leukemia, and paroxysmal nocturnal hemoglobinuria, is required for its diagnosis [29].

Aplastic anemia is connected with significant morbidity, resulting in a worse quality of life and premature mortality [30]. Persistent neutropenia makes you more vulnerable to potentially deadly infections, whereas thrombocytopenia can lead to catastrophic bleeding in key organs [31]. Chronic iron overload caused by recurrent red cell transfusion eventually results in multi systemic dysfunctions such as cardiomyopathy, endocrinopathies, and liver siderosis [32].

Pathogenesis

For many years, an immune-mediated etiology has been proposed for aplastic anemia since immunosuppressive therapy is frequently effective in the treatment of aplastic anemia and aplastic anemia patients' bone marrow lymphocytes may inhibit normal bone marrow in vitro [28]. Several studies have found increased cytokine production, low CD4 T regulatory cells, oligoclonal CD8 cytotoxic T cells, and, to a lesser extent, proliferation of particular CD4 cell populations in aplastic anemia patients' bone marrow [31]. Coupled with the recent discovery of acquired copy number neutral loss of hetero-zygosity of the short arm of chromosome 6, representing a likely genetic signature of immune escape,10 these

findings have strengthened the belief that bone marrow aplasia in acquired aplastic anemia is immune mediated, with the term "immune-mediated aplastic anemia" replacing the conventional term "idiopathic aplastic anemia" [33].

Pernicious anemia

Pernicious anemia is the hematologic expression of chronic atrophic gastritis of the stomach corpus, which depletes the gastric mucosa of gastric parietal cells. Asymptomatic autoimmune gastritis, a chronic inflammatory disease of the stomach mucosa, occurs 10-20 years before the development of corpus atrophy [34].

Two key biologics are produced by gastric parietal cells: intrinsic factor and HCL acid. Pernicious anemia is caused by intrinsic factor deficiency and a neutralizing intrinsic factor antibody, which inhibits cobalamin absorption. Iron deficiency anemia develops 20 years before cobalamin-deficient pernicious anemia. The laboratory diagnosis is based on parietal cell antibody with or without intrinsic factor antibody, cobalamin-deficient megaloblastic anemia, and increased serum gastrin due to acid secretion failure [35].

Megaloblastic anemia

Megaloblastic anaemia is brought on by defective DNA synthesis in hematopoietic progenitors, which leads to insufficient erythropoiesis—the production of red blood cells—and intramedullary hemolysis. Leukopenia and thrombocytopenia are also frequent, but macrocytic anaemia with an elevated mean corpuscular volume (MCV), described as more than 100 fL, distinguishes megaloblastic anaemia. The prevalence of macrocytosis in the general community can reach 4%, whereas megaloblastic anaemia only makes up a small portion of cases. Non-megaloblastic reasons of macrocytic anaemia include ethanol addiction, myelodysplastic syndrome, aplastic anemia, hypothyroidism, liver disease, and medications. Although these causes are associated with increased MCV, they do not lead to the other megaloblastic anaemia symptoms.Vitamin B12 or folate deficiencies are the most typical reasons of megaloblastic anaemia (cobalamin) [36].

Microcytic anemia

Microcytic anemia are those that are distinguished by the production of smaller-than-normal red blood cells. The diminutive size of these cells is attributed to diminished synthesis of hemoglobin, the main ingredient of red blood cells. A lack of globin product (thalassemia), limited iron delivery to the heme group of hemoglobin (anemia of inflammation), a lack of iron delivery to the heme group (iron-deficiency anemia), and deficiencies in heme group synthesis are the causes of microcytic anemia [47].

Developmental domains

Motor development

Iron deficiency is likely to have an impact on motor development via two main mechanisms:

- Altered basal ganglia function as a result of dopaminergic changes.
- The myelination of the motor cortex and surrounding areas has been compromised.

Both of these mechanisms are primarily activated in late gestation and early infancy [37]. It discovered some evidence that iron supplementation during early infancy (0-6 months of age) promotes motor development, whereas iron supplementation later in infancy or early childhood may be less beneficial [38]. These findings support the hypothesis of timing-dependent impact and suggest that iron status up to six months of age may be especially important for motor development [39].

Socio-emotional development

This review article expected to find a link between ID and socio-emotional development based on the strong evidence from animal studies. However, the evidence for this relationship was not as strong as anticipated. This could be due to a lack of age- and setting-appropriate tools, which has previously been identified as a limitation in the field . Furthermore, examiner-reported behavior during an assessment was the most common type of socio-emotional assessment [37,40]. This measure, however, is neither affect-specific nor representative of naturalistic behavior. Finally, even when the same tool was used, there was no consistency in the reporting of socio-emotional outcomes across studies. When multiple assessments were performed, agreement was low, indicating a lack of reliability [41]. The reported connections between smoking during pregnancy and reduced linear growth may reflect numerous recognized biological pathways that may contribute to poor development of the fetus and early kid, either directly or indirectly [48].

Cognitive development

The evidence linking iron status and cognitive development was ambiguous [38]. Given that iron is more important in some aspects of cognition than others, the lack of association could be due to the broad assessments used in most studies (e.g., the BSID, MSEL, and WPPSI), which combine many aspects of cognition, such as memory, language, attention, and fine motor skills, into a single total score [42]. Studies that used mechanistic evidence-based tests, such as those related to processing speed, memory, or executive function, were able to identify a relationship between iron status and outcomes, suggesting that they were more sensitive to iron-related neural changes. Furthermore, given the extended period of cognitive development, behavioral deficits associated with ID in early development may become more apparent with age. The age cut off for outcome measures may have limited our findings [37].

Brain development

The mechanisms underlying iron deficiency's impact on brain development are unknown. Beard proposed that iron deficiency could impair myelination during critical stages of brain develop-

ment; Lozoff emphasized the importance of protecting the developing brain from the negative effects of iron deficiency. Iron deficiency anemia in childhood is linked to delayed psychomotor development. Children who had severe, ongoing iron deficiency as infants score worse on tests of their mental and motor skills and are more likely to suffer long-term developmental setbacks, such as learning challenges and socioemotional issues [43]. Iron supplementation trials in developing countries revealed benefits, particularly for motor development and social-emotional behaviour [39,44]. Despite being consistently observed, global outcomes provide little insight into the specific CNS processes impacted by iron deficiency anemia in infancy [43]. Anemia in newborn babies can range from asymptomatic to a life-threatening event. It is fatal if left untreated. Severe anemia has a significant impact on cerebral tissue oxygenation due to its effect on the oxygen-carrying capacity of blood. Chronic hypoxia exposure in animal models has been linked to white matter injury and developmental delay [45].

Conclusion

Anemia is a prevalent condition in infants, particularly in developing countries. The condition can have a detrimental impact on cognitive, motor, behavioral, and physical development during infancy. The effects of anemia can persist into later childhood and adulthood, highlighting the importance of early prevention and treatment. Preventing and treating anemia in infants is crucial to ensure optimal growth and development. Interventions aimed at improving maternal health and education on proper nutrition can help prevent anemia in infants, iron supplementation and improved nutrition can help reduce the risk of anemia and promote optimal development in infants.

Conflicts of Interest

Authors declare that there is no conflict of interest.

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