کۆلێژی پەروەردە – بەشی بایۆلۆجی

ناوی مامۆستایانی سەرپەرشتیار و ناوی قوتابیان بۆ پرۆژەی توێژینەوەی پۆلی چوارەم/ ساڵی خوێندنی ٢٠٢٣-٢٠٢٤

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زانکۆی سەڵاحەدین-هەولێر

Salahaddin University –Erbil

(Differential Diagnosis of Hypochromic Microcytic Anemia in Pregnant Women)

Research Project

Submitted to Department of (Biology) in partial fulfillment of the requirements for the Degree of BSC. In (Biology)

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2024-April

Dedication

To begin with, I thank (Allah) for His blessing, which made me able to complete and perform this study with success, the lord of the universe, blessing, and peace be on Muhammad (Allah's peace and prayers be upon him), I would like thanks to my supervisors (Prof. Dr. khabat anwer ali) for suggesting this topic and giving me useful instruction throughout studying period, I express my deepest appreciation for this academic staff of Biology department…..

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Abstract

Anemias are classified on the basis of size of the RBCs. This review describes the common types—iron deficiency anemia, thalassemia, anemia of chronic inflammation, and sideroblastic anemia. as well as the clinical and laboratory findings in each. h. Diagnosis depends on the CBC, cell morphology (as observed on the peripheral blood smear. Levels of iron, total iron binding capacity, free erythrocyte protoporphyrin, and ferritin in serum, as well as electrophoretic separation of hemoglobins may also be included. On completion of this article, the reader will be able to identify the common types of microcytic anemias—iron deficiency anemia, thalassemia, anemia of chronic inflammation, and sideroblastic anemia during pregnancy.

Keywords: Hypochromic, Microcytic, Anemia, Pregnant.

Introduction

Anemia is the global public health problem affecting the 1/3 rd of the world's population with major consequences for human health and affecting social and economic development. Children and pregnant women are more vulnerable groups to anemia. Geographically, those living in Asia and Africa are at the greatest risk. (Sharief and Patima, 2022).

The causes of microcytic anemias are diverse and include iron deficiency, thalassemia, chronic inflammation, and sideroblastic anemia (Meredith and Rosenthal,1999).

Anemia, a decrease in the number of red blood cells (RBC) or hemoglobin concentration (Hb) in the blood, is a serious pathological condition. It is characterized by such symptoms as fatigue, weakness, we4e5rrdizziness, drowsiness, and dyspnea (Aringazina et al.,2023).

The World Health Organization states that anemia is the 10 biggest health problem in the modern century, where 40% of pregnant women in the world experience anemia

due to the increased need for iron that occurs during pregnancy. Anemia in pregnancy is called potential danger to mother and children (potentially harmful to mother and child), that's why anemia requires serious attention from all parties involved in health services at the forefront. Anemia has a significant impact on the health of the mother and fetus, it interferes with the delivery of oxygen across the placenta to the fetus and interferes with normal intrauterine growth, leading to fetal death and perinatal death (Sharief and Patimah, 2022).

For Disease Control and Prevention (Centers for Disease Control and Prevention) has defined anemia in which the hemoglobin is less than 11 g/dL in the first and third trimesters, and less than 10.5 g/dL in the second trimester. In conditions that require a lot of iron, pregnancies that occur in very young or very old women will be susceptible to anemia. The younger and older the age of a pregnant mother will affect the nutritional needs needed. Lack of fulfillment of nutrients during pregnancy, especially at the age of<20years and >35years will increase the risk of anemia. A pregnant woman at risky age, which is<20years, there will be food competition between the fetus and the mother who is still in the process of growth. Pregnant women aged<20years tend not to be ready to support the need for additional red blood cells for the fetus, while the need for iron in the body is quite a lot for the growing period of the fetus and pregnant women. Mothers who become pregnant at the age of 35 years, have entered the early degenerative phase, so that body functions are not optimal and experience various health problems. Pregnancy under the age of 20 and above 35 years is a pregnancy that has a risk of anemia (Sharief and Patimah , 2022).

Table 1. Anemia classification according to MCV and reticulocytosis*

Microcytic*	**Regenerative (RPI ≥ 3)** Iron deficiency anemia under treatment - Congenital or corpuscular hemolytic anemias (spherocytosis, thalassemia, sickle cell disease)	**Arregenerative (RPI <2)** Iron deficiency anemia - Chronic infection / inflammation - Lead poisoning
Normocytic*	- Extracorpuscular hemolytic anemia (hypersplenism, microangiopathy, drugs, infections) - Corpuscular hemolytic anemia - Acute bleeding	- Medullary aplasia - Spinal infiltration - Aplastic crisis or transient erythroblastopenia in corpuscular hemolytic anemia - Infectious anemia - Chronic kidney disease
Macrocytic*	- Hemolytic crisis in AIHA with marked reticulocytosis	- Folic acid or vitamin B12 deficiency - Fanconi anemia - Blackfan-Diamond anemia - Liver disease - Myelodysplastic syndrome - Sideroblastic anemia - Hypothyroidism

*Always adjust MCV according to age and sex for each patient (Table I). AIHA: autoimmune hemolytic anemia. RPI: reticulocyte production index. Adapted from: San Román S, Mozo Y, 2017.

The Differential Diagnosis 0f Hypochromic Microcytic Anemia Can Be

1- Thalassemias

Thalassemia trait (TT) are the most common conditions of microcytic hypochromic anemia (MHA) (Xiao et.al., 2021) .The term "thalassemia" refers to hemoglobinopathies characterized by partly or completely suppressed synthesis of one of the two types of polypeptide chains (α or β) as a result of missense/nonsense mutations (single-base substitutions) or frameshift mutations of the genes controlling the structure of the hemoglobin-protein chains in one or both "allelic" globin genes, providing decreased hemoglobin concentration, microcytosis , and anemia. Depending on the genes affected, the resulting defect, and the corresponding effect on the globin chain, several types of thalassemia have been described, the most common types of clinical importance being α-, β/δ-, and β-thalassemia (Petrakos et al.,2016).

The α-globin chain synthesis begins in fetal life. The responsible genes – four in total – are situated in two genetic loci in chromosome 16. Gene deletion or less commonly mutation results in α-thalassemia, and phenotype depends on the affected gene number. When all four genes are affected (-/-|-/-) in homozygous α-thalassemia,fetal synthesis of α-chains is impossible, leading to an excess of γ-chains and forming the unstable Bart's hemoglobin (γ4), which is incapable of oxygen exchange. The affected fetuses sustain severe anemia, cardiomegaly, and hydrops fetalis, and ultimately intrauterine or neonatal death. When three genes are affected (α-/-/-), α-chain synthesis is restricted to a minimum. The existence of two α-genes (α-thalassemia trait) is expressed as a mild hypochromic microcytic anemia. Globin synthesis is still unbalanced, leading to hemolysis and iron overload. In α0 -thalassemia, the two deleted genes belong to the same allele (-/-|α/α), and this is prevalent among Asian and Eastern Mediterranean populations, while in α+ -thalassemia, prevalent among African people, the deleted genes belong to different homologous chromosomes. In "silent" carriers, only one α-gene is affected (α/-|α/α), and the three functional remaining ones are capable of normal hemoglobin production (Petrakos et al.,2016)

β-Thalassemia is extremely heterogeneous in terms both of genotype and phenotype, depending on the nature of β-gene mutation and the extent of impairment in β-globin chain production. As a rule, heterozygous carriers of β-thalassemia (one affected allele), are asymptomatic, and only altered laboratory values (low, normal, or slightly subnormal hemoglobin levels, slightly low mean cellular hemoglobin, low mean cell volume, low β: α-globin chain ratio on biosynthesis, HbA2 3.5%) are observed (Petrakos et al.,2016).

diagnosis of thalassemia

Hemoglobin electrophoresis remains the gold standard for the diagnosis and classification of thalassemia. Quantitative evaluation of HbA2 can be made by either electrophoresis or by high-pressure liquid chromatography (Petrakos et al.,2016).

Treatment of thalassemia

1- Maternal transfusion: treating anemia that requires regular blood transfusions and extensive ongoing medical care (Akther,2016). In general, nontransfused women with hemoglobin 8 g/dL at the 36th week of gestation should be advised not to initiate blood transfusions, and erythropoietin administration could be an alternative. Hemolytic alloantibody and erythrocyte-autoantibody development complicates transfusion therapy in thalassemia patients as the rate of red blood-cell alloimmunization following one single blood-unit transfusion is (1–1.6) %, while the rate in patients receiving regular blood transfusions may be as high as 60%. (105–107) Alloantibodies crossing placenta can cause fetal and/or neonatal hemolytic anemia, making extended genotype and antibody screening necessary before transfusion, and if transfusion is necessary, fully phenotyped matched blood should be given (Petrakos et al.,2016).

2-Women should be advised to modify their lifestyle and diet, avoid smoking and alcohol, and start taking supplements of folic acid, calcium, and vitamin D. Before and throughout pregnancy, as well as during breast-feeding, adequate calcium and vitamin D intake and bisphosphonate interruption is mandatory, as both are negative calcium-balance states. Especially for thalassemic women, often osteoporotic and vitamin D-

deficient, vitamin D levels should be optimized before pregnancy and thereafter maintained within the normal range. Folate demand in pregnancy is normally increased, and all thalassemic women are advised to receive folic acid supplementation at a dose of 5 mg/day, in order to prevent fetal neural tube defects, as well as a significant increase in predelivery hemoglobin level,130 and in heterozygous cases to prevent superimposed megaloblastic anemia (Petrakos et al.,2016).

2-Sideroplastic Anemia

Sideroblastic anemia (SA) is a diverse group of disorders that are characterized by anemia of varying severity and unified pathologically by an abnormal accumulation of iron in the mitochondria of the red cells precursors with impaired heme synthesis. The singular feature that characterizes all forms of SA and is required for initial diagnosis is the presence of iron-laden mitochondria forming a perinuclear ring around the nucleus of the erythroblast, visualized by Prussian blue staining of the bone marrow aspirate smear. To be designated as ring sideroblasts, the International Working Group on Morphology of Myelodysplastic Syndrom recommended that ring sideroblasts should have a minimum of five granules in a perinuclear distribution; these granules could either surround the entire nucleus, be localized to portions of the perinuclear area, or cover at least one-third of the nucleus. The unique pathology in SA can be primarily linked to defects in the heme biosynthesis, and Fe-S biogenesis pathways, as well as the impaired synthesis of mitochondrial and cytosolic proteins essential for heme synthesis. These defects end in the build-up of iron granules rather than the normal incorporation of iron into the protoporphyrin IX (PPIX) in the mitochondrion. Sideroblastic anemia is a rare event in pregnancy. Sideroblastic anemia is conventionally classified as congenital sideroblstic anemia (CSA) or acquired sideroblastic anemia (ASA) (Mohamed et al.,2023).

Congenital SA is mostly hypochromic microcytic with decreased MCV reflecting a reduction of heme synthesis in the erythroid precursors. In our literature search, we came across very limited reports on sideroblastic anemia in pregnancy, mostly as case reports that have shown the relationship between the toxic effect of orally administered

sex hormones or pregnancy alone, and secondary sideroblastic anemia. All the above were thought of within the differential diagnosis as a possible cause for the anemia in the current reported case and were thoroughly investigated. The absence of family history, dysplasia, SF3B1 mutation, and the strict association of anemia with pregnancy, make CSA and clonal SA unlikely in our case. Likewise, the normal results for copper, zinc, and lead with the absence of a history of alcoholism or medication linked to SA exclude these acquired causes. The low pyridoxin level was implicated as the cause of recurrent anemia because of increased requirements during pregnancy. (Mohamed et al.,2023)

Diagnosis of Sideroblastic During Pregnancy

Specifying the type of SA is rather challenging as it requires extensive workup including deep genetic testing. However, a careful review of the patient's constellation of clinical findings and red cells indices and morphology aid in narrowing the differential diagnosis. Identification of possible revisable causes that can be treated as a pyridoxin deficiency is crucial to avoid both maternal and fetal adverse effects like prematurity, abortions, and even fetal death, especially with Hb drop to a critical level. (Mohamed et al.,2023)

Treatment of Sideroblastic During Pregnancy

Pyridoxal phosphate the active form of vitamin B6 plays an essential role in ALAS2 enzymatic activity, which catalyzes the condensation of glycine and succinyl

coenzyme A to form 5-aminolevulinic acid (ALA), the first and rate-controlling enzyme of heme synthesis. (Mohamed et al.,2023).

3- anemia of chronic disease

Anemia of chronic disease, also known as secondary anemia is the most common hematological disorder of the erythropoietic line after iron deficiency anemia in the world. There is a permanent increase in the incidence of this type of anemia which is associated with the aging of the population and the tendency to develop chronic

diseases, mainly malignant tumors and chronic kidney disease. Its incidence varies from 40% in patients with solid tumors and reaches almost 100% among patients with leukemia or lymphoma. It was proven that anemia significantly worsens the quality of life of patients with chronic diseases, and in some types of cancer (lung cancer, locally advanced head and neck squamous cell carcinomas, cervical cancer) is an independent adverse prognostic factor. It is currently assumed that there are several mechanisms leading to overt anemia of chronic diseases (Wiciński et al.,2020).

Because of the long circulating lifespan of mature erythrocytes, HRC values mainly provide information of the iron status during the last four months. Hypochromic red blood cells show lower erythrocyte deformability and shortened lifespan so increased levels of HRC cause aggravation of anemia. Consequently, the reduction of hypochromic red blood cells plays an important role in the effective correction of anemia. On the other hand, as reticulocytes have a lifespan of one to two days in circulation, changes in the CHr identify variations in iron demand to bone marrow more rapidly. The determination of the percentage of hypochromic red cells or reticulocyte hemoglobin content can be useful in detecting accompanying iron restricted erythropoiesis in patients with anemia of chronic disease (Amstad Bencaiova et al.,2017).

The measurements of hypochromic red blood cells (HRC), the reticulocyte hemoglobin content (CHr), and red blood cell distribution width (RDW) provide an accurate description of hemoglobinization of red blood cells and reticulocytes we identified anemia of chronic disease with reduced iron stores but with normal level of hypochromic erythrocytes (HRC < 2.5%), normal reticulocyte hemoglobin content (CHr >28 pg), normal red blood cell distribution width (RDW < 15%), and low serum EPO levels for the grade of anemia (serum EPO < 50 U/l by Hb < 10 g/dl) (Amstad Bencaiova et al.,2017).

Exclusion criteria were anemia of other etiology (i.e., vitamin B12 deficiency, folic acid deficiency, hemoglobinopathy, etc.), liver or kidney disease, and multiples. Women with mean corpuscular hemoglobin (MCH) ≤25 pg, mean corpuscular volume

(MCV) ≤75 fl, and percentage of microcytic erythrocytes (MRC) ≥3% were tested for hemoglobinopathies (Amstad Bencaiova et al.,2017).

Treatment of Chronic Disease

According to hemoglobin level at the start of the therapy, the women were treated either with intravenous iron and rhEPO or with intravenous iron only twice weekly as described elsewhere (Amstad Bencaiova et al.,2017).

4- Iron Deficiency Anemia

Iron is one of the most important microelements of the body necessary for the synthesis of hemoglobin. Absorption of iron in the gastrointestinal tract is a complicated process involving many proteins (DMT1 protein, ferroportin, ferritin, hepcidin, hephaestin, transferrin, lactoferrin). The stored iron can be divided into active (ferritin) and inactive (hemosiderin) pools. The percentage of the body's normal iron content is estimated at 65% in hemoglobin, (3-5) % in myoglobin and 0.5% in heme enzymes. The rest of the iron content is 30% in the form of iron stored in (liver, spleen and bone marrow) in the form of Two ferrites and hemosiderin, as the normal ratio of iron stored in the form of two ferrets to that stored in the form of hemosiderin. Ferritin is the main chemical compound of stored iron. Ferritin is mainly in the cytoplasm of endothelial reticulum cells and hepatocytes, and a few of them are in epiblasts in the bone marrow. Ferritin It is a major iron storage protein, essential for iron homeostasis and involved in a wide range of physiological and pathological processes (Salam and Mohsin ,2021).

Hepcidin expression increases in response to elevated iron levels while it is inhibited by erythropoiesis, iron deficiency and tissue hypoxia in response to signals originating in bone marrow, liver and possibly muscle tissue and adipocytes. In the event of an iron deficiency, the transcription of hepcidin is inhibited, which facilitates

the absorption of iron and the release of iron from the body's stores (Salam and Mohsin ,2021).

The daily diet provides an average of (10–15) mg of iron, of which only (5–10) % (i.e., 1 mg) is absorbed into the body. The human body uses (20–25) mg of iron daily for hemoglobin synthesis. Most of this element comes from the natural degradation of erythrocytes due to their damage or aging (Wiciński et al.,2020).

The most common causes of anemia are poor nutrition, deficiencies of iron, micronutrients deficiencies including folic acid, vitamin A and vitamin B12 (Di Renzo et al.,2015).

Iron deficiency anemia occurs much more often in women than in men. According to various estimates, about 20% of women suffer from Iron deficiency anemia. Anemia is a condition characterized by a decrease in hemoglobin in the blood (< 130 g/l for men and < 120 g/l for women) (Abdurasulovich,2023).

Iron deficiency is the most widespread nutritional deficiency in the world and it accounts for 75% of all types of anemia in pregnancy (Di Renzo et al.,2015).

Diagnosis

Anemia diagnosis should begin with a CBC including blood smear evaluation. Hematology instruments provide abundant automated enumerations such as reticulocyte counts, but many diagnoses will be missed without blood smear evaluation. Instrument graphics can illustrate changes in erythrocyte populations well. If the diagnosis is not obvious from the history, physical examination, and CBC, then additional testing is indicated. Additional tests are chosen based on the situation, species, and probability of different causes of anemia for a location (Tvedten, 2022).

Serum erythropoietin, folate, and vitamin B12 levels were measured using the Immulite 1000 chemiluminescent assay normal ranges, (5.4-31) mIU/mL, (9.53-45.17) nmol/L, and (177.1-664.2) pmol/L, respectively). Iron metabolism was analyzed in terms of serum iron level (normal range 9-30 μmol/L), transferrin level

(normal range 2-3.6 g/L), transferrin saturation (TSAT) (calculated from serum iron and transferrin concentration; normal range 25.1- 51.9%), and ferritin level (normal range 13-400 ng/mL). Serum hepcidin was measured using ELISA (Chen et al., 2023). The following iron metabolism markers were studied for all subjects: serum iron (Fe), total serum iron-binding capacity (TIBC), latent serum iron-binding capacity (LIBC), and serum ferritin (SF) were studied (Aringazina et al.,2023).

Table 2. biochemical parameter

no	Tested markers	Reference values	Anemia marker
1	Fe concentration, µmoll/L	12.5-32	<12.5
2	Latent iron binding capacity, µmoll/L	24.2-70.1	>70
3	Total iron binding capacity, µmoll/L	41-77	>77
4	Hepcidin**, ng/mL	1.49-41.46	<1.49
5	Ferritin, ng/mL	10-120	<10iron deficiency anemia >120 anemia of the chronic inflammation

Table3.

No	Morphological Parameters*		
	Tested markers	Reference values	Anemia marker
	Hematocrit, %	33-45.0	<33
2	Hemoglobin, g/L	110-155	<110
3	RBC number, million/μL	3.8-5.10	<3.8
4	Mean corpuscular volume, fL	80.0-100	<80
5	Red cell distribution, %	11.6-14.8	>14.8
6	Mean corpuscular volume, pg	27.0 -34.0	<27
7	Mean Corpuscular Hemoglobin Concentration, g/dL	34.0-36.0	<34

Treatment of iron deficiency anemia

It has also been recently proposed an iron and folic acid supplementation program for the prevention of anemia in pregnancy with different characteristics according to the population to be treated (Di Renzo et al.,2015).

Folic acid is a vitamin, belonging to group B, essential for DNA synthesis and for a physiological development of neural tube. During pregnancy, the folate requirement increases with the growth of the fetus, and a deficiency of this vitamin can cause megaloblastic anemia. For this reason, it has also been recently proposed an iron and folic acid supplementation program for the prevention of anemia in pregnancy with different characteristics according to the population to be treated (Di Renzo et al.,2015).

Oral iron replacement therapy with gradual replenishment of iron stores and restoration of hemoglobin is the preferred treatment. Formulations may contain either the bivalent ferrous form or the trivalent ferric form, with the consideration that

bivalent iron preparations are easily absorbed compared with the trivalent formulations (Di Renzo et al.,2015).

Parenteral iron therapy, given either by intramuscular or intravenous route, may be used if anemia is moderate or severe, if oral therapy has failed or in case of mild anemia, oral route is not tolerated or the patient tolerance is low (Di Renzo et al.,2015).

Iron supplementation given through the best route of administration. More often, oral ferrous iron formulations are used, due to their effectiveness and low cost Parenteral treatment should be isolated to treat moderate and severe cases of anemia, when a rapid iron supplementation is needed (Di Renzo et al.,2015).

Intravenous iron therapy is a safe alternative since it is able to reduce the need for blood transfusion (Di Renzo et al.,2015).

The effectiveness of ferric carboxymaltose for treatment of iron deficiency anemia, increasing levels of Hb and improving iron stores, and with good tolerability. Ferric carboxymaltose represents a new formulation for intravenous iron treatment, which, it has been demonstrated, can be used at high doses (up to 1000 mg) with better toleration and effectiveness, during second and third trimester of pregnancy, and with fewer side effects compared with iron sucrose formulation, also when the dose is double. demonstrated a linear decrease in maternal anemia with higher doses of iron, up to 66 mg/daily. It has been demonstrated that these doses of iron were associated with a linear increase in birth weight and decrease risk of low birth weight, as well as positive, linear dose–response relation with risk of maternal anemia, indicating a benefit of giving higher, up to 66 mg/day, rather than lower doses. Contrarily, the recommended daily dose for treatment of manifest iron deficiency anemia is at least 120–200 mg/day up to 1000 mg/day, as demonstrated for ferric carboxymaltose (Di Renzo et al.,2015).

Table 3. the marker examined during the study – reference values indicator of anemia.

TEST	IRON DEFICIENCY ANEMIA	THALASSEMIA	ANEMIA OF CHRONIC DISEASE	SIDEROBLASTIC ANEMIA
SIDEROBLASTIC ANEMIA	Decreased	Increased	Normal to increased	Normal to increased
Red blood cell distribution width	Increased	Normal to increased	Normal	Increased
Serum iron level	Decreased	Normal to increased	Normal to decreased	Normal to increased
Total iron binding capacity	Increased	Normal	Slightly decreased	Normal

conclusion

In my research paper determine the differential diagnosis of hypochromic microcytic anemia in pregnant women such as the impact of sideroblastic anemia, thalassemia, iron deficiency anemia, chronic disease on pregnant women and classification of anemia. Diagnosis depends on the CBC, cell morphology (as observed on the peripheral blood smear). The aim of my research diagnosis type of microcytic anemia and treatment during pregnancy.

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