Silent Anemia in Pregnancy

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ABSTRACT

Keywords: Anemia, Pregnancy, Thalassemia.

Anemia is a condition in which the number of red blood cells or the hemoglobin concentration within them is lower than normal. Thalassemia is a Mutation of the globin gene that can cause changes in the globin chain, e.g. structural hemoglobinopathy or changes in the rate of synthesis or the production ability of certain globin chains. Epidemiological research in Indonesia found that the frequency of the beta thalassemia gene ranges from 3-10%. Case report of patient Mrs. T, 27 years old, HPHT: 01-10-2023, routine ANC examination every month, ANC examination results in 18-19 weeks no complaints, and laboratory examination results in Hb 4.7. Patients with thalassemia beta major and intermediate need to be given regular transfusions and keep their hemoglobin levels above 10 mg/dl. All patients with homozygous thalassemia should receive folic acid supplements.

Introduction

Anemia is a condition in which the number of red blood cells or the hemoglobin concentration within them is lower than normal. Haemoglobin is needed to carry oxygen and if you have too few or abnormal red blood cells or not enough hemoglobin, there will be a decreased capacity of the blood to carry oxygen to the body’s tissues. This results in symptoms such as fatigue, weakness, dizziness, and shortness of breath, among others. The optimal hemoglobin concentration required to meet physiologic needs varies by age, sex, elevation of residence, smoking habits, and pregnancy status (SUDIARTA, RIZKA, RIZAL, ABIGAIL, & PRATAMA, 2022). Anemia may be caused by several factors: nutrient deficiencies through inadequate diets or inadequate absorption of nutrients, infections (e.g. malaria, parasitic infections, tuberculosis, HIV), inflammation, chronic diseases, gynecological and obstetric conditions, and inherited red blood cell disorders. The most common nutritional cause of anemia is iron deficiency, although deficiencies in folate, vitamins B12, and A are also important causes (Sanif & Husin, 2017).

Anemia is a serious global public health problem that particularly affects young children, menstruating adolescent girls and women, and pregnant and postpartum women. WHO estimates that 40% of children 6–59 months of age, 37% of pregnant women, and
30% of women 15–49 years of age worldwide are anemic (Budiardjo & Irwiensyah, 2015).

Hemolytic anemia is a lack of hemoglobin levels due to the breakdown of erythrocyte cells faster than the bone marrow’s ability to replace them. Based on the involvement of immunoglobulins in hemolysis events, hemolytic anemia is divided into immune hemolytic anemia and non-immune hemolytic anemia. In immune hemolytic anemia, hemolysis occurs due to the involvement of antibodies, usually IgG or IgM that are specific to erythrocyte antigens (autoantibodies). Meanwhile, in non-immune hemolytic anemia, hemolysis occurs without the involvement of immunoglobulins, such as molecular defect factors, membrane structure abnormalities, hemoglobinopathy, etc., which do not include immunological mechanisms. Thalassemia itself is included in one of the types of hemoglobinopathy.

Haemoglobinopathy is a disorder caused by impaired hemoglobin synthesis due to mutations in or near globin genes. Mutations in globin genes can cause changes in globin chains, e.g. structural hemoglobinopathy or changes in the rate of synthesis or the ability to produce certain globin chains called thalassemia (Guntur et al., 2014).

Thalassemia is a defect or damage to hemoglobin (Hb) due to mutations or deletions of genes that regulate the formation of alpha or beta globin chains that are usually autosomal recessively derived (Daniel et al., 2019). In Southeast Asia, symptomatic anemia occurs at 0.66 per 1,000 births with an incidence of 20,420 per year and is almost entirely dependent on transfusions (Sandjaja, Nafisa, & Manurung, 2020). Beta thalassemia is commonly found in Mediterranean populations, while alpha thalassemia is commonly found in Asian and African populations (Mishra, Lakhera, Negi, & Pandey, 2022). In the world, thalassemia beta is widely distributed in Mediterranean populations, the Middle East, India, Pakistan, Southeast Asia, Southern Russia, and China, and is rarely found in Africa except Liberia, and some parts of North Africa are sporadic in all races. As for alpha thalassemia, it is widely distributed from Africa to the Mediterranean, the Middle East, East Asia, and Southeast Asia (Guntur et al., 2014).

Thalassemia is a hereditary disease or genetic disorder due to red blood cell abnormalities that result in patients having to undergo blood transfusions throughout their lives. Thalassemia is a genetic disease that has the most types and frequencies in the world with varying clinical manifestations. Data from the World Bank shows that 7% of the world's population is a carrier of thalassemia. Every year about 300,000-500,000 babies are born with severe hemoglobin abnormalities, and 50,000 to 100,000 children die from thalassemia. Indonesia is one of the countries with a high frequency of genes or carriers of thalassemia. Epidemiological research in Indonesia found that the frequency of the thalassemia beta gene ranges from 3-10% (National Guidelines for Thalassemia Management Medical Services, 2018). Based on data from the Thalassemia Indonesia Foundation, there has been a continuous increase in thalassemia cases. From 2012 to June 2021, there were 10,973 cases of thalassemia in Indonesia (Sehat Negeriku Editorial, 2022).
According to (Rediayanto, 2023) states that thalassemia is differentiated into alpha thalassemia if the synthesis of the alpha globin chain decreases and thalassemia beta if there is a decrease in the synthesis of the beta-globin chain. Thalassemia can occur from mild to severe (Wishnuwardhana, Fernandez, Trixie, Jovito, & Gabriella, 2022). Beta thalassemia is inherited from both parents who carry thalassemia and shows the most severe clinical symptoms, this condition is also called thalassemia major. Patients with thalassemia major will experience anemia due to the destruction of hemoglobin and patients have to undergo a lifetime blood transfusion once a month. Thalassemia cases in Madiun City number 39 people.

**Method**
The method used is a case report.

**Results and Discussion**
Case report of patient Mrs. T, 27 years old, HPHT: 01-10-2023, routine ANC examination every month, ANC examination results in 18-19 weeks no complaints, and laboratory examination results in Hb 4.7. The patient's previous disease history was transfused when he was still in high school with 1 blood bag with complaints of frequent dizziness, and then never transfused again. The patient was treated at Dr. Soedono Madiun with G1POA0 18/19 weeks + Severe Anemia (Hb 4.7).

Weight 44.7 kg, Height 155 cm. Vital signs of blood pressure 120/80 mmHg, Breath rate 20 x/min, pulse 110 x/min, temperature 36.7 °C, SpO2 99% room water. Physical examination found anemis in the conjunctiva of the eye.

**Status Obstetri**
- Inspection: Distended abdomen, no surgical scars, stria gravidarum (-)
- Leopold I: teraba ballotement. TFU: 14 cm
- Leopold II: the ballotement. DJJ: 150x times/minute
- Leopold III: teraba ballotement
- Leopold IV: not yet entered the upper door of the pelvis
- Fetal motility: There is fetal movement
  - His: (-)
  - VT: VT Ø -/ eff 0% /ket (-)/kep/SSmell/H-I
  - DJ: 150 x/min

The ANA test was negative. Hematology examination showed Ferritin 821.7 (Hyperferritin), Hematocrit 16.3% (Hypohematocrit), Erythrocytes 2.24 (low), MCV 72.8 (low), MCH 22.3 (low), MCHC 30.7 (low), Reticulocytes 10.7 (increased). Peripheral blood deletion indicates the conclusion of Hypochrome microcytic severe anemia with an elevated erythropoietic system, a suspect of iron differentiation with
active bleeding or hemolytic processes. Blood chemistry test of total Bilirubin 3.05 (increased), Bilirubin decreased by 1.10 (increased).

Thalassemia is an inherited disorder syndrome and is included in the hemoglobinopathy group, which is a disorder caused by disruption of hemoglobin synthesis due to mutations in or near the globin gene. This mutation in the globin gene can cause two changes in the globin chain, namely:

Changes in the structure of the amino acid chains of certain globin chains called structural hemoglobinopathy, or Changes in the rate of synthesis or the ability to produce certain globin chains, are called thalassemia.

Adults have HbA hemoglobin consisting of alpha globin 2 and beta 2 chains, while fetuses have HbF consisting of alpha 2 and gamma 2 globin chains (Paloma, 2023). The decrease in beta globin chain production in beta thalassemia increases alpha globin chain production resulting in an excess of alpha globin chain. Beta globin chains in adults and gamma globin chains that are still produced after birth cannot bind to the entire overproduced alpha globin chain, so excess alpha globin chains are characteristic of the pathogenesis of beta-thalassemia.

A study of 48 thalassemic women β showed that 72.9% of transfusion-dependent patients during pregnancy, 18.75% ended up in premature labor, 14.5% of patients underwent cesarean delivery, 45.8% of patients experienced fetal growth restriction and 8.3% of pregnancies ended in stillbirth. The patient's and family's history is very important in diagnosing thalassemia because, in populations with certain races and ethnicities, there is a high frequency of specific types of abnormal thalassemia genes. On physical examination, symptoms and pale signs are found that indicate abnormal cell pooling, and skeletal deformity, especially in beta-thalassemia which shows expansion of the bone marrow cavity, in thalassemia major.

Excessive alpha chains that cannot bind to other globin chains will precipitate precursors of blood cells in the bone marrow and progenitor cells in peripheral blood, causing impaired maturation of erythroid precursors and erythropoiesis and causing erythrocyte lifespan to be shortened. The activity is anemia. Anemia causes continuous proliferation of erythroid precursors in the bone marrow resulting in bone marrow expansion which then leads to skeletal deformities and various growth and metabolic disorders. Furthermore, anemia also results in splenomegaly so that more abnormal blood cells are trapped and then destroyed by the phagocyte system. Bone marrow hyperplasia then leads to increased iron absorption and load. In addition, regular transfusions carried out by thalassemia patients will also increase the iron load so that there is iron accumulation in various organ tissues which will be followed by organ damage and end with death if this iron is not immediately removed (Guntur et al., 2014).

Hemoglobinopathy found clinically, whether in children or adults, is caused by mutations in the globin α or β gene. Meanwhile, mutations in the weight of globin genes ζ, ε, γ can cause death at the beginning of gestation.

A decrease in the synthesis rate or production capacity of one or more globin chains a or b, or other globin chains, may cause a partial or complete production defect of the
globin chain. As a result, thalassemia occurs which is of the type according to the globin chain whose production is disrupted, as shown below (Daniel et al., 2019). Thalassemia α occurs due to reduced or no production at all of the production of globin chains α.

1. Thalassemia β occurs due to reduced or no production at all of the production of globin chain β.

2. Thalassemia σβ occurs due to reduced or no production at all of the production of both globin chains σ and β.

3. Double heterozygous thalassemia α or β with hemoglobin thalassemia variant.

Patients with thalassemia have a history that varies from asymptomatic to clear complaints of anemia. There is a family history, of complaints of weakness, enlargement of the liver and spleen, growth disorders, sexual maturity disorders, and heart failure (Maulina, 2018). In alpha thalassemia, there are two main phenotypes. The elimination of the fourth α-globinogen chain (−/−) characteristic homozygous α-thalassemia. Because the chain forms fetal hemoglobin, the fetus in the womb is affected. Without α-globin chains, Bart’s hemoglobin and H hemoglobin are formed as abnormal tetramers. Fetal death occurs either in the womb or immediately after birth.

Homozygous alpha thalassemia is a common cause of hydrops fetalis in Southeast Asia. HbH(β4) diseases are compatible with extraterine life. Abnormal red cells at birth contain a mixture of Bart hemoglobin, H hemoglobin, and hemoglobin A. Neonates appear both at birth but soon develop hemolytic anemia. Some of Bart's hemoglobin present at birth is replaced postnatally by hemoglobin H. The disease is characterized by hemolytic anemia, which may be severe and similar to α-thalassemia major. Anemia in women usually worsens during pregnancy.

Deletion of two clinically occurring genes in α-thalassemia minor, which is characterized by minimal to moderate hypochromic microcytic anemia. Thus, the genotype may be -/- or -/. Patients with β thalassemia intermedia are at increased risk of complications during pregnancy, which include, worsening anemia and thrombocytopenia, miscarriage, intra-uterine fetal death, premature labor, cesarean section, and intrauterine growth restriction (Nassar et al., 2006). There is no specific therapy for β-thalassemia minor during pregnancy. Prophylactic iron and folic acid are administered. Prenatal diagnosis of thalassemia using chorionic villus sampling can be done at 9 to 13 weeks.

In order for a pregnancy to occur normally, what must be considered is that women with thalassemia must have an optimal health status and not experience organ damage (heart, liver, and others) due to excess iron. Liver function and heart function tests are done before planning a pregnancy. Diet is also considered so as not to consume foods that contain excessive iron.

Pregnant patients with thalassemia beta minor do not need to be given specific therapy and generally tolerate pregnancy well. Iron supplementation is given if there is an indication, while folic acid is recommended to be given when planning a pregnancy or immediately after pregnancy. If anemia becomes severe. Then the administration of transfusions can be considered. Patients with thalassemia beta major and intermediate
need to be given regular transfusions and keep their hemoglobin levels above 10 mg/dl. All patients with homozygous thalassemia should receive folic acid supplements. Therapy of iron chelation with deferoxamine in pregnancy is still controversial. Female patients suffering from alpha thalassemia HbH, in general, can have a good pregnancy, but often cause acute exacerbations of chronic anemia and require blood transfusions.

**Conclusion**

Patients develop severe hypochromic microcytic anemia characterized by a low red blood cell count (low erythrocytes), a small average red blood cell volume (low MCV), and a low hemoglobin concentration per red blood cell (low MCHC), accompanied by hyperferitinemia (very high ferritin levels) and increased reticulocytes indicating an increase in red blood cell production by the bone marrow in response to anemia. An increase in total and indirect bilirubin levels indicates the presence of excessive breakdown of red blood cells, while high reticulocytes indicate that the bone marrow responds rapidly to anemia, which is consistent with hemolysis. Hyperferitinemia usually indicates the presence of iron hoarding, but in the context of anemia and very high ferritin levels, this can indicate a problem with the efficient use of iron in the body. This disorder may be caused by the inability of the alpha globin chain to bind to other globin chains, leading to the deposition of alpha chains in erythroid progenitor cells in the bone marrow and red blood cells in peripheral blood, resulting in impaired maturation of red blood cells (erythropoiesis) and shortening the lifespan of red blood cells. Despite a negative ANA test, autoimmune hemolytic anemia should still be considered due to an indirect increase in reticulocytes and bilirubin, while globin production disorders such as thalassemia, especially alpha thalassemia, and sideroblastic anemia can also cause similar symptoms and laboratory results. To ensure a proper diagnosis, it is recommended to carry out further examinations such as direct and indirect Coombs tests to evaluate the presence of antibodies that cause hemolysis, hemoglobin analysis (hemoglobin electrophoresis) to evaluate the possibility of thalassemia or other hemoglobinopathy, and bone marrow biopsies to assess the status of erythropoiesis and the presence of abnormal cells or iron deposits. With a more precise diagnosis, appropriate therapy can be given to overcome anemia and improve the patient's quality of life.
Bibliography


