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Anemia in Pregnancy: A Pragmatic Approach

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Importance: Anemia is common in pregnancy, ranging from 5.4% in developed countries to more than 80% in developing countries. Anemia in pregnancy has been associated with prematurity, low birth weight, and adverse pregnancy outcomes.

Objective: This review uses clinical vignettes to illustrate the clinical presentations, approach to diagnosis, maternal and fetal implications, and treatment for the common etiologies of anemia in pregnancy.

Evidence Acquisition: Literature review.

Results: Normal physiological changes in pregnancy result in alterations of hematological parameters particularly in a reduction of hemoglobin (Hb) concentration. Consequently, the Hb used to define anemia in pregnancy is lower than in nonpregnant patients. As there is an increased requirement of iron in pregnancy, it is not unexpected that iron deficiency remains the most common cause of anemia and warrants a preemptive approach to prevent a further reduction in Hb. The syndromes associated with microangiopathic hemolytic anemia may pose a diagnostic challenge, as there are several potential etiologies that may be difficult to differentiate, and microangiopathic hemolytic anemia can be associated with significant maternal and fetal morbidity and mortality. Anemia secondary to sickle cell disease and autoimmune hemolytic anemia merit special attention because there are risks secondary to red blood cell transfusion and risks to withholding transfusion.

Conclusions and Relevance: Anemia in pregnancy is potentially associated with maternal and fetal adverse outcomes. Providing evidence-based care is essential to achieving the best pregnancy outcomes.

Target Audience: Obstetricians and gynecologists, family physicians.

Learning Objectives: After completing this activity, the learner should be better able to describe the normal physiological changes in hematological parameters in pregnancy, recognize common and potentially life-threatening diseases manifested as anemia, and develop an approach to anemia in pregnancy.

Anemia is common in pregnancy.[1] The prevalence of anemia during pregnancy ranges from 5.4% in the United States to more than 80% in developing countries.[1,2]

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The World Health Organization defines anemia as a hemoglobin (Hb) level less than 130 g/L in men and less than 120 g/L in nonpregnant women. In pregnancy, anemia during pregnancy has been defined as an Hb concentration less than 110 g/L, as less than 105 g/L in the second and third trimesters, and as less than 100 g/L postpartum, owing to the increase in plasma volume that occurs during pregnancy.[3]

To a degree, a reduction in the Hb concentration during pregnancy is a result of normal physiological changes. Plasma volume during pregnancy increases

by approximately 50%.[4] The changes in plasma volume expansion begin as early as 6 weeks' gestational age, progressively increasing to a peak at 32 weeks' gestation, and is thought to be due to hormone-mediated vasodilation and subsequent activation of the renin-angiotensin-aldosterone system.[4] During pregnancy, angiotensinogen rises with estrogen production, together with increased vasopressin, leading to salt and water retention.[5] Red blood cell (RBC) mass also increases in pregnancy, although to a lesser degree compared with plasma volume. The increase in RBC mass results from an increased erythropoietin level in response to circulating progesterone and placental lactogen.[4,5] The disproportionate increase in plasma volume to RBC mass leads to a decreased Hb and hematocrit levels, more evident from the second trimester to delivery.[4,6]

Anemia in pregnancy has been associated with prematurity, low birth weight, and adverse pregnancy outcomes.[7] Accurate identification of the etiology of anemia and its satisfactory management are integral to optimizing the pregnancy and delivery outcomes for this population. Clinical cases are used to approach to common etiologies of anemia in pregnancy and their treatment.

Case 1

A 25-year-old gravida 3 para 2 who is asymptomatic at 34 weeks' gestational age has an Hb concentration of 62 g/L, mean corpuscular volume (MCV) 60 fL (79–97 fL), white blood cells 10×10^9/L, and absolute reticulocyte count 100×10^9/L (reference range, 41–88 $\times 10^9$/L). Peripheral blood film shows microcytic anemia. She has never received a transfusion prior to pregnancy.

Microcytic Anemia

Thalassemia. Adult Hb consists predominantly of HbA composed of α and β globin. Adult Hb also consists of a small proportion of HbA_2 ($\alpha 2\delta 2$) and HbF ($\alpha 2\gamma 2$). Thalassemia refers to the reduced production of α and/or β globin chains due to mutations in the α and/or β globin genes. The laboratory parameters suggestive of thalassemia consist of a microcytic, hypochromic anemia in ethnic populations with established increased risk of thalassemia, such as in regions of Africa, the Middle East, the Mediterranean, Southeast Asia, Caribbean, South America, and the Western Pacific.[8] Pregnant patients of ethnic origins where thalassemia occurs, who have a microcytic hypochromic anemia, should be screened for hemolgobinopathies.[8] If a hemoglobinopathy is confirmed, partner screening will enable the assessment of risk of fetal inheritance of the condition.[8]

Iron Deficiency. With the marked increase in iron demands in pregnancy, iron deficiency occurs commonly in pregnancy, 18% of pregnancies, and ranges from 7% in the first trimester and 30% in the third trimester.[1,9,10] The total iron requirement is approximately 1.2 g in pregnancy, with the highest requirement in the third trimester, up to 7.5 mg daily.[11] Dietary iron is known to be inadequate to meet the iron requirement in pregnancy.[11] Daily iron dietary intake should be greater than 27 mg/d to meet the iron requirement in pregnancy, assuming 25% bioavailability.[11] This translates to approximately 1.5 lb of cooked beef and 4.5 lb of cooked chicken, amounts difficult to incorporate into the daily diet.[12] All healthy pregnant women are advised to take a prenatal multivitamin and mineral supplement containing 16 to 20 mg of iron per day to achieve daily iron requirements.[12] Common available prenatal vitamins in North America contain 27 to 35 mg of elemental iron per tablet (Table 1).

Symptoms of iron deficiency during pregnancy are nonspecific. Pica cannot be used to characterize iron deficiency during pregnancy, as pica is more prevalent in pregnant women regardless of iron status.[13] Fatigue is also a nonspecific and common symptom, as is dyspnea with exertion, particularly in the third trimester. A ferritin concentration of less than 30 μg/L is diagnostic of iron deficiency in pregnancy.[3] Although soluble transferrin receptor is another sensitive measure of iron status, it is not widely available.[3] Patients with increased risk of iron deficiency include those with a multiple pregnancy or consecutive pregnancies within 1-year interval.

Because of the high prevalence of iron deficiency anemia, a complete blood count at 12 and 28 weeks' gestation and a trial of oral iron in patients who are asymptomatic, with an Hb concentration less than 110 g/L in the first trimester and less than 105 g/L in the second trimester (with a normocytic or microcytic anemia in the absence of a hemoglobinopathy), followed by an assessment of response after 2 weeks have been suggested.[3] Patients who refuse blood for religious reasons should have iron indices assessed even in the

TABLE 1
Common Iron Preparations

Preparation	Dosage Form	Elemental Iron, mg
Ferrous gluconate	Tablet	35
Ferrous sulfate	Tablet	65
Ferrous fumarate	Capsule/tablet	100
Polysaccharide-iron complex	Capsule/powder	150
Heme-iron polypeptide	Tablet	11
Prenatal vitamin	Tablet	27–35

absence of anemia. Oral iron supplements result in a rise of approximately 20 g/L in the Hb concentration over 3 to 4 weeks, in the absence of ongoing losses or increasing demand. Intermittent oral iron supplementation is likely a feasible alternative with fewer adverse effects compared with daily oral therapy in nonanemic patients.[14]

Parental iron therapy should be considered if there is a lack of response to oral iron supplementation, intolerance to iron supplementation, severe anemia, or advanced gestation.[3] Compared with oral therapy, parenteral iron has been shown to cause a faster rise in Hb levels and is associated with less gastrointestinal adverse effects,[15,16] but the effect on neonatal outcome is still limited.[17] Parenteral iron is not considered an option in the first trimester or if there has been a severe or anaphylactic reaction to parenteral iron.[3]

Treatment of iron deficiency will result in an increase in the maternal Hb concentration, which may result in a reduction of exposure to RBC transfusion and the risk of alloimmunization. The effect of the treatment of iron deficiency on maternal quality of life needs to be further defined, as does the effect of the treatment of iron deficiency on fetal outcomes.[18,19]

Case 1 Resolution

The plasma ferritin concentration was 7 (7–128 μg/L), plasma iron 4 μmol/L (8–26 μmol/L), total iron binding capacity 114 μmol/L (50–90 μmol/L), and transferrin saturation 0.04 (0.1–0.4). Her low ferritin level alone is adequate to diagnose iron deficiency anemia.[3] As her Hb concentration was 62 g/L, and she was at 34 weeks' gestation, parenteral iron therapy was instituted to obtain a more rapid rise in her Hb concentration, so as to reduce the risk of the need for RBC transfusion.

Case 2

A 34-year-old gravida 1 para 0, at 28 weeks' gestational age, was hospitalized because of hypertension and proteinuria. With the exception of an elevated body mass index at 40 kg/m^2, there was no other significant medical history. She had an asymptomatic mild elevation in blood pressure since 21 weeks' gestational age that did not require antihypertensive agents. At hospitalization, her blood pressure was 140/100 mm Hg. She had a protein-creatinine ratio of 90 mg/mmoL (0–30 mg/mmoL) on a random urine sample. Her Hb concentration was 90 g/L (115–160 g/L), platelets 300 $\times$ 10^9/L (150–400 $\times$ 10^9/L), and creatinine was 55 μmol/L (55–100 μmol/L). Two days following admission, she developed a severe headache and epigastric pain. She had normal mentation, but her blood pressure increased to180/110 mm Hg. She experienced tenderness to palpation in the right upper quadrant and epigastrium and had mild bilateral pitting edema. The Hb concentration decreased to 70 g/L, leukocytes were 13.9 $\times$ 10^9/L, platelets 75 $\times$ 10^9/L, aspartate aminotransferase 287 U/L (≤32 U/L), alanine aminotransferase 221 U/L (≤33 U/L), lactate dehydrogenase (LDH) 608 U/L (≤214U/L), total bilirubin was 30 μmol/L (3.4–17.1 μmol/L), and haptoglobin was undetectable (0.26–2.26 g/L). Peripheral blood film showed polychromasia, megathrombocytes, neutrophilia, and schistocytes.

Microangiopathic Hemolytic Anemia

Microangiopathic hemolytic anemia (MAHA) is characterized by intravascular mechanical fragmentation of RBCs leading to schistocytes on the peripheral blood film, thrombocytopenia, and organ dysfunction.[20] Microangiopathic hemolytic anemia can occur in pregnancy for a variety of reasons listed in Table 2.[20–23]

Preeclampsia

Approximately 2% of all pregnancies are complicated by preeclampsia.[24] Preeclampsia is a systemic disorder most commonly characterized by new-onset hypertension (≥140/90 mm Hg) after gestational week 20 and new onset of 1 or more of proteinuria (defined

TABLE 2
Disorders Associated With Microangiopathic Hemolytic Anemia[23]

Primary Thrombotic Microangiopathy Syndromes	Other Disorders
Hereditary disorders	Systemic infection
ADAMTS13 deficiency-mediated TMA (also known as TTP)	Systemic cancer
Complement-mediated TMA (also known as atypical HUS)	Severe preeclampsia, eclampsia, HELLP syndrome
Metabolism-mediated TMA (eg, B_{12} deficiency)	Severe hypertension
Acquired disorders	Autoimmune disorders (eg, systemic lupus erythematosus, systemic sclerosis, antiphospholipid antibody syndrome)
ADAMTS13 deficiency-mediated TMA (also known as TTP)	Haematopoietic stem cell or organ transplantation
Shiga toxin–mediated TMA (also known as Shiga toxin-HUS)	
Drug-induced TMA	
Complement-mediated TMA	

HUS indicates hemolytic uremic syndrome.

as ≥0.3 g/d in a 24-hour urine collection or ≥30 mg/mmol urinary creatinine by urinary protein/Cr ratio in pregnancy[25]). It is now recognized that absence of proteinuria does not rule out the disease[25,26]; in these patients, preeclampsia can be defined as hypertension and organ involvement such as renal insufficiency, liver disease (elevated transaminases and/or severe right-upper-quadrant or epigastric pain), neurological disease (seizures [eclampsia], persistent visual disturbances, stroke), and/or hematological disorders (thrombocytopenia, disseminated intravascular coagulation), pulmonary edema, and/or fetal complications including intrauterine growth restriction or stillbirth.[25–27]

Hemolytic anemia, elevated liver enzymes, and low platelets (HELLP) is the most common cause of MAHA in pregnancy and represents a severe manifestation of preeclampsia.[28] Ten percent to 20% of patients with preeclampsia may have HELLP syndrome,[29] which is often accompanied by right-upper-quadrant or epigastric pain, whereas hypertension and proteinuria may be mild or absent.[30] HELLP predominantly occurs in the third trimester; however, 30% of women may present within 48 hours postpartum.[31,32] The perinatal mortality rate is high, between 7% and 34%.[33] Preeclampsia and HELLP resolve within days to months after delivery.

Delivery is the treatment for HELLP syndrome with transfusion support of platelets if needed.[26,33] Corticosteroids have not been shown to improve clinical outcomes.[25,26,32] If HELLP does not improve or deteriorates after 3 days postpartum, has onset more than 7 days postpartum, or is accompanied by persistent or worsening neurological or renal dysfunction, an alternative diagnosis such as a primary thrombotic microangiopathy (TMA) must be considered.

ADAMTS13-Deficient TMA (Thrombotic Thrombocytopenic Purpura)

Compared with HELLP syndrome, pregnancy-associated thrombotic thrombocytopenic purpura (TTP) occurs less frequently, with an estimated frequency during pregnancy or postpartum of less than 1 per 100,000 pregnancies, compared with 0.29 per 100,000 nonpregnant adults per year.[20,28,34] A marked reduction in ADAMTS13 activity (<10%) and presence of anti-ADAMTS13 autoantibodies will establish the diagnosis of acquired TTP, whereas the absence of ADAMTS13 antibodies suggests hereditary TTP.[35,36] Hereditary TTP is secondary to homozygous or compound heterozygous mutations of ADAMTS13.[20] A mild reduction in ADAMTS13 levels in the absence of other findings may also occur with normal pregnancy.[37]

Hereditary TTP may precede the pregnancy or occur during pregnancy. A considerable proportion of patients with hereditary TTP may encounter the onset of symptoms during pregnancy.[38] Twenty-four percent of patients with hereditary TTP had the first presentation in pregnancy in comparison to less than 5% of patients with acquired TTP.[38] The maternal survival rate in the absence of neurological or renal complications has been demonstrated to be 88% (95% confidence interval, 75%–95%),[38] although survival has not been shown to be affected in other reports.[35] Hereditary TTP occurs with similar rates in each trimester.[35] Third-trimester or postpartum presentation of hereditary TTP has been associated with higher fetal survival, whereas diagnosis in the first trimester has been inconsistently associated with poorer outcomes.[35,38] Plasma infusion, every 2 weeks at pregnancy onset until 20 weeks, then weekly until delivery, in subsequent pregnancies, has been shown to decrease the risk of fetal demise.[35,38]

Similar to hereditary TTP, second-trimester presentation of acquired TTP also seems to be associated with increased fetal mortality.[35] Preconceptual counseling for subsequent pregnancies at high-risk maternity centers with assessment of ADAMTS13 levels may identify patients at high risk of recurrence who may benefit from alternative therapy, such as rituximab, prior to pregnancy.[35] Subsequent pregnancies following pregnancy-induced TTP or adult-onset TTP are followed with at least monthly ADAMTS13 levels and at least monthly hematological parameters with consideration of instituting plasma exchange when ADAMTS13 levels decrease to less than 10%.[35]

Thrombotic thrombocytopenic purpura during pregnancy is a medical emergency. Plasma infusion is used as a replacement for ADAMTS13 for hereditary TTP, whereas plasma exchange and immune suppressants (eg, corticosteroids) are used for acquired TTP.[35] Antenatal use of low-dose aspirin and low-molecular-weight heparin has been recommended in patients with platelet counts greater than 50×10^9/L, but is not considered a standard regimen. Serial ultrasound scans for fetal growth and well-being should be instituted in the late second and third trimesters, given the risk of intrauterine growth restriction and intrauterine fetal demise.[35]

Differentiating HELLP from TTP may be difficult especially if there is concurrent acute kidney injury, which can occur in up to 50% of patients with HELLP syndrome.[39,40] In addition, preeclampsia or HELLP and TTP may coexist, imparting a higher risk of maternal mortality compared with TTP in the absence of the preeclampsia spectrum (44% vs 21%, respectively).[41,42] Maternal angiogenic factors such as sFlt-1:PIGF ratio have been investigated for the prediction of preeclampsia;

however, the assays are not available widely and may lack specificity.[43,44] The classic pentad of thrombocytopenia, MAHA, fever, renal dysfunction, and neurological symptoms that has been considered diagnostic for TTP may occur in only 40% of cases.[45] In pregnancy, TTP frequently presents with atypical symptoms, such as gastroenteritis and headaches, which pose a diagnostic challenge.[34,35]

Distinguishing features of TTP and HELLP include the trimester at presentation. Pregnancy-associated acquired TTP occurs predominantly in the late second or early third trimester, with median onset at 24 weeks.[42] In comparison, only 10% of patients with HELLP present prior to 27 weeks' gestation.[46] Concurrent TTP and HELLP occur later in pregnancy than TTP without any evidence of preeclampsia/HELLP (29 ± 8 vs 24 ± 9 weeks, $P < 0.05$) and have lower total LDH–to–aspartate aminotransferase ratio compared with TTP alone (13:1 vs 29:1).[42] Thrombocytopenia is more severe, that is, less than 20×10^9/L, and fragments are more pronounced in TTP compared with HELLP.[34]

Complement-Associated TMA

Other disorders associated with MAHA and thrombocytopenia, such as complement-associated TMA (atypical hemolytic uremic syndrome), occur less frequently in pregnancy. Complement-associated TMA predominantly occurs postpartum, and renal involvement tends to be more common.[47] Because it can be difficult to distinguish from TTP, plasma exchange remains the first-line treatment. If a patient does not respond to plasma exchange, or the ADAMTS13 level is normal, then complement-associated TMA is suspected, and a complement inhibitor, such as eculizumab, is considered. There is limited experience with eculizumab use during pregnancy.[48,49] Eculizumab was found in a small study to be able to traverse the placenta in minimal amounts; however, eculizumab was not shown to affect fetal complement activation and organ development, and it was not detected in breast milk.[49] The risk of recurrence of complement-associated TMA in subsequent pregnancies is approximately 20%.[47]

Case 2 Resolution

ADAMTS13 level was slightly reduced but not diagnostic of TTP; thus, presentation was more consistent with HELLP syndrome. The patient underwent urgent cesarean delivery on the same day because of fetal distress and HELLP syndrome. Within 1 week, hematological and biochemical parameters recovered, in the absence of further intervention.

Case 3

A 33-year-old gravida 1 para 0 with sickle cell (SS) disease was hospitalized at 22 weeks' gestation with a painful vaso-occlusive crisis. Her Hb was 81 g/, MCV 91 fL, and platelets 179×10^9/L. Total plasma bilirubin was 40 μmol/L, and indirect bilirubin was 30 μmol/L.[1–16] Hemoglobin decreased to 58 g/L the following day, and the absolute reticulocyte count was 216.8×10^9/L ($10–90 \times 10^9$/L). Total bilirubin peaked at 60 μmol/L and was composed of predominantly indirect bilirubin. Haptoglobin level was less than 0.3 g/L (0.6–2.7 g/L). Plasma LDH was 706 U/L. Chest radiograph was unremarkable.

Sickle Cell Disease

The SS syndromes include HbSS, HbSC, and HbSβ^0. HbS, which results from the production of structurally abnormal β globin chains, polymerizes in deoxygenated regions of the circulation, resulting in occlusion of the microvasculature and acute and chronic organ dysfunction. Women with SS disease not infrequently enter pregnancy with chronic complications such as frequent vaso-occlusive painful crises, frequent need for RBC transfusion, and osteopenia. In addition, pregnant women with SS disease experience increased rates of maternal and fetal/neonatal complications,[50–55] including increased risk of infection, vaso-occlusive painful crises, thrombosis, and maternal mortality,[50,51] as well as higher rates of preterm delivery, preeclampsia, and small-for-gestational-age infants.[50,51,55]

Red blood cell transfusion has been shown to reduce certain complications in nonpregnant patients with SS disease patients such as stroke and, when administered preoperatively, postoperative acute chest syndrome[56,57]; however, the role of RBC transfusion in pregnancy with SS disease has not been well defined because the risk of alloimmunization may be increased not only with SS disease with vaso-occlusion but also because of pregnancy.[58,59] Aside from RBC transfusion, there are limited options for patients with SS disease. A recent systematic review concluded that prophylactic RBC transfusion may improve maternal and fetal outcomes, although its conclusions are tempered by small sample sizes of the included studies and lack of data from high-quality randomized clinical trials in pregnancy.[60] Thus, the decision to institute prophylactic RBC transfusion in pregnancy must take into consideration the limitations of available evidence in the context of the risk of alloimmunization. As patients with SS disease have a propensity to develop alloantibodies, if RBC transfusion is required, RBCs should be matched for Rhesus and Kell antigens if the patient is not

alloimmunized and extended matching in the presence of alloantibodies.[61,62]

Of the 2 hematinics that are routinely used in pregnancy, folic acid is prescribed to all patients with SS disease; however, iron supplementation may not be required because patients may have iron overload. Iron supplementation is reserved for patients with laboratory evidence of iron deficiency.[62] If folic acid has not been prescribed prior to pregnancy, the standard for all pregnant women, it should then be prescribed during pregnancy at a dose of 5 mg daily.[62]

Case 3 Resolution

The patient was hydrated and administered supplemental oxygen. Her obstetrical ultrasound was unremarkable. Her vaso-occlusive pain was adequately managed with analgesics. After 72 hours, her Hb concentration stabilized, and her vaso-occlusive pain and hemolytic parameters began to improve. She was discharged following 5 days of hospitalization and did not receive an RBC transfusion.

Case 4

A 35-year-old woman gravida 2 para 1 was referred with asymptomatic macrocytic anemia: Hb 75 g/L with MCV of 106 fL at 28 weeks' gestation. Her last pregnancy was unremarkable, without cytopenias, and she had had a normal vaginal delivery. She did not have symptoms of autoimmune disease and did not have a family history of anemia or autoimmune disease. Liver enzymes were within the reference range. The reticulocyte count was 200×10^9/L, and haptoglobin level was less than 0.07 g/L (0.26–2.26 g/L). Total bilirubin was mildly elevated at 32 μmol/L, predominantly secondary to an elevation of indirect bilirubin. The ferritin level was 37 μg/L, and vitamin B_{12} and folate levels were normal. Blood film showed mild spherocytosis. Abdominal ultrasound revealed a normal spleen size. The direct antiglobulin test (DAT) showed immunoglobulin G (IgG) autoantibodies. Ultrasound of the fetus demonstrated normal growth.

Macrocytic Anemia

A slight physiological macrocytosis occurs during normal pregnancies due to increased erythropoiesis.[63–65] In healthy pregnancies, MCV can rise from 85 to 90 fL, but a higher rise, reaching 96 to 102 fL, has also been observed in the third trimester.[63] This physiological macrocytosis may mask iron deficiency in pregnancy.[65]

A DAT with IgG antibodies, with or without hemolysis, may occur in 1% to 15% of hospitalized patients.[66] A DAT with IgG antibodies and hemolysis may occur in patients with warm autoimmune hemolytic anemia (AIHA), following the use of intravenous immune globulin, with drugs such as methyldopa, and with infectious mononucleosis.[66] Pregnancy is associated with the development of IgG autoantibodies in 0.1% of the population, but generally these autoantibodies are not associated with hemolysis and are not associated with maternal or fetal adverse outcomes.[67]

Autoimmune hemolytic anemia, as characterized by RBC destruction caused by autoantibodies, has been reported to occur at least 4 times more frequently during pregnancy than in the nonpregnant population, although it remains an infrequent occurrence.[68,69] Autoimmune hemolytic anemia may be secondary to warm (IgG autoantibodies), cold agglutinin disease, or a mix of warm and cold autoantibodies.[70] Autoimmune hemolytic anemia may be accompanied by immune thrombocytopenia (Evans syndrome),[71] and pregnancy has also been reported to precipitate hemolytic anemia where the hemolysis resolves postpartum.[72,73] As warm AIHA is secondary to IgG antibodies, the fetus is potentially at risk of hemolysis, as IgG antibodies can traverse the placenta, although hemolytic disease of the fetus and newborn precipitated by AIHA is uncommon. Routine fetal ultrasound surveillance, including measurements of the middle cerebral artery peak systolic velocity, can provide reassurance of the absence of fetal anemia.

Corticosteroids are the standard treatment for AIHA, although the optimum dose has not been determined, either in pregnant or nonpregnant patients.[74,75] The doses used range from 1 to 1.5 mg/kg daily, with a standard response seen within 2 weeks of initiation in nonpregnant patients.[75] Corticosteroids may be associated with a small risk of orofacial clefts during embryogenesis and may aggravate maternal hypertension or diabetes later in pregnancy.[76,77] Lower doses may be tried to reduce adverse effects. The efficacy of intravenous immunoglobulin for the treatment of AIHA is variable, and most data are from case series in nonpregnant patients.[74] Intravenous immunoglobulin is administered in the same dose as for nonpregnant patients, 1 to 2 g/kg in over a 2- to 5-day interval.[74]

Second-line therapies for AIHA in pregnancy, such as splenectomy, azathioprine, or cyclosporin, have not been studied widely, but have been reported for the use of immune thrombocytopenia in pregnancy. Rituximab has been used for immune thrombocytopenia during pregnancy but may be associated with neonatal B cell suppression if used within 6 months of delivery, and its safety in pregnancy has not been definitively established.[23,78]

Red blood cell transfusion is reserved for symptomatic anemia and is of temporary benefit. Red blood cell

autoantibodies may mask the presence of alloantibodies, and the provision of RBCs for these patients may be delayed.[75] Alloantibodies can potentially result in delayed hemolytic transfusion reactions and hemolytic disease of the fetus and newborn.

Case 4 Resolution

The patient's laboratory parameters are consistent with warm AIHA. No secondary causes of AIHA, such as systemic lupus erythematosus, drugs, viral infections, or lymphoproliferative disease, were identified. She responded to prednisone at 0.5 mg/kg daily, and her Hb concentration increased to 100 g/L prior to delivery. Her anemia and macrocytosis resolved 6 weeks postpartum.

CONCLUSIONS

Normal physiological changes affect hematological parameters during pregnancy, and hence maternal anemia is common.[2,79,80] Management is tailored according to the etiology, yet there are limited data to provide an optimal approach to treatment. Further research is needed to establish evidence-based treatment strategies for anemia management in pregnancy.

Patient Consent

The cases are hypothetical.

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