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CHAPTER 2

Megaloblastic Anemia in Pregnancy

Niharika Dhiman, Anjali Deshpande

INTRODUCTION

Anemia in pregnancy is the most commonly affecting medical disorder. According to the National Family Health Survey-4 (NFHS-4) the incidence varies as per the maternity status—58% of breastfeeding women are anemic as compared to 50% of females who are pregnant.[1] Megaloblastic anemia constitutes about 25% of the anemia in pregnancy in developing countries.

Megaloblastic anemia is described as a group of anemia caused by impaired deoxyribonucleic acid (DNA) synthesis. It is characterized by presence of macroovalocytes on peripheral smear and abnormal finding of megaloblastic hyperplasia in the bone marrow sample.[2] Addison in 1849 first characterized it as anemia, general lethargy, and debility.[3] In 1877, Osler and Gardner noted its association with neuropathy, following which in 1887 Lichtheim documented its association with myelopathy. Ehrlich was the first one to demonstrate megaloblasts.

METABOLISM OF FOLIC ACID AND VITAMIN B_{12}

Folic acid (pteroylglutamate) functions in its active form tetrahydrofolate. The dietary sources of folic acid include green leafy vegetables, fruits (banana, lemon, oranges, and melons), cereals, nuts, beef, meat, fish, liver, and kidney. It is heat labile and is destroyed by overcooking.

Folic acid absorption occurs in the small intestine. Majority of it is absorbed both actively and passively in the jejunum by binding to reduced-folate transporter-1 and 2 (RFT-1, 2) and folate-binding protein (FBP). A small part of it is absorbed passively in the ileum. Folic acid is absorbed in its monoglutamate form from the enterocytes where it is converted to methyltetrahydrofolate and transported into the systemic and enterohepatic circulation. Intracellularly methyltetrahydrofolate is converted into its active and functional form tetrahydrofolate. Part of the intracellular methyltetrahydrofolate is utilized in the synthesis of thymine which is one of the four pyrimidine bases of DNA. In case of folic acid the above thymine synthesis does not occur and uracil is incorporated in place of thymine thus altering the DNA structure and leading to abnormal nuclear maturation.[4]

TABLE 1: Recommended daily allowance for folic acid and vitamin B_{12}.

Group	*Folic acid (µg)*	*Vitamin B_{12} (µg)*
Reproductive age	400	2
Pregnancy	600	2.6
Lactation	500	2.6

The main source of cobalamin or cyanocobalamin is animal food, plant food does not contain cobalamin. Vitamin B_{12} is absorbed from the digestive system in three stages. In stomach it binds to R protein and transported to the duodenum and jejunum. In the alkaline pH of duodenum and jejunum R protein is degraded and cobalamin binds to intrinsic factor (IF). This stable IF-cobalamin complex is taken up by the enterocytes of ileum where IF is degraded and cobalamin binds to transcobalamin II (TCII) binding protein and enters the systemic circulation. Intracellularly cobalamin exists in two active forms—(1) methylcobalamin and (2) adenosylcobalamin. Methylcobalamin acts as a coenzyme in synthesis of tetrahydrofolate and methionine, this is the common pathway for biological action of both cobalamin and folic acid. In case of cobalamin deficiency methyltetrahydrofolate cannot be demethylated for methionine synthesis moreover it cannot be polyglutamized to keep it anchored to the cell as a result it escapes into the circulation without being used. This is also called as *folate trap/Methyltetrahydrofolate trapping.*[5]

Adenosylcobalamin acts as a coenzyme in conversion of methylmalonyl to succinic acid, accumulation of methylmalonyl in a state of cobalamin deficiency has been attributed to the development of neuropathy.[6]

The recommended daily allowance has been shown in **(Table 1)**.

ETIOPATHOGENESIS

Megaloblastic anemia is primarily caused by deficiency of folic acid and vitamin B_{12} which can be due to dietary deficiency or any other factors hampering its absorption **(Table 2)**.

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TABLE 2: Etiological factors for megaloblastic anemia.

Causes of folic acid deficiency	*Causes of vitamin B_{12} deficiency*
Dietary deficiency: Malnutrition, alcohol consumption, goat milk intake	Strict vegetarians
Absorption problems: Celiac disease, Crohn's disease, tropical sprue, Whipple's disease, diabetes mellitus, amyloidosis, small bowel resection	Pernicious anemia, partial gastrectomy, *Helicobacter pylori* infection, gastritis
Drugs: Trimethoprim, pyrimethamine, phenytoin, valproic acid, antiretroviral drugs	
Liver disease, hypothyroidism and chronic hemolytic disease	

Megaloblastic anemia is result of ineffective erythropoiesis which is caused by lack of formation of thymine; it is one of the pyrimidine bases required for DNA synthesis. Uracil is incorporated instead of thymine which alters the structure of pure DNA. As a result the damaged DNA is repaired by p53 cellular apoptosis process. This leads to asynchronous maturation between the nucleus and the cytoplasm leading to release of immature erythropoietic precursors as blasts into the circulation.

Megaloblastic anemia caused by folic acid deficiency usually presents latter half of the pregnancy (20–28 weeks) when the stores are depleted, occurs commonly in multiple pregnancies. It may also present during the puerperium up to 5 months postpartum [oral contraceptive pill (OCP) users/antiepileptic drugs].[7]

Pernicious anemia caused by IF deficiency leading to failure of absorption of vitamin B_{12} is rarely found during pregnancy as most of these women present with infertility.

CLINICAL MANIFESTATION

The clinical features of megaloblastic anemia are insidious in onset; the features of vitamin B_{12} deficiency develop over years. It usually presents with features of anemia syndrome, i.e., easy fatigability, weakness, lassitude and breathlessness. Gastrointestinal problems leading to megaloblastic anemia may also present with nausea, vomiting, reflux, gastritis and diarrhea. Cobalamin deficiency leads to specific neurological features which include paresthesia, hypoesthesia, tingling in toes and fingers, gait abnormalities, muscle weakness. These neurological symptoms mostly affect the lower extremities. These neurological symptoms have been attributed to the demyelination and gliosis of the gray column caused by methionine deficiency and accumulation of methylmalonic acid which causes subacute combined degeneration of posterior and lateral gray column of spinal cord. A role of elevated tumor necrosis factor alpha and epidermal growth factor has also contributes to the neurological effects.[8]

On examination the following features are seen in megaloblastic anemia—pallor, change of hair color, glossitis, hyperpigmentation of skin and nails, however features of koilonychia and platynychia are not seen in megaloblastic anemia. Petechial rash over skin can be seen in cases of megaloblastic anemia with thrombocytopenia. Such cases need to be differentiated from aplastic anemia and leukemia. Splenomegaly is found in 10–15% of cases.

On neurological examination signs of vitamin B_{12} deficiency reveal a positive Romberg's and Babinski sign, presence of spasticity, hyporeflexia, and clonus.

LABORATORY DIAGNOSIS

The basic workup of megaloblastic anemia includes: complete blood count, flow cytometry, peripheral blood smear, serum folate, and vitamin Cobalamine levels **(Table 3 and 4)**.

Flow cytometry: Macrocytes are found >75% of the cases. Mean corpuscular volume (MCV) > 100 fL (mild: 100–105, moderate: 106–115, and severe >116 fL), mean corpuscular hemoglobin (MCH) > 33 pg, and normal mean corpuscular hemoglobin concentration (MCHC). Red cell distribution width (RDW) is increased.

TABLE 3: Criteria for diagnosis of megaloblastic anemia.[8]

Criteria for diagnosis of megaloblastic anemia (the hemoglobin level should be below10 g% and at least two out of five should be present):

1. More than 4% of neutrophil polymorphs have five or more lobes.
2. Orthochromatic macrocytes with diameter > 12 mm.
3. Presence of Howell–Jolly bodies
4. Nucleated red blood cells (RBCs)
5. Presence of macropolycytes (giant polymorphs within buffy coat layer)

TABLE 4: Specific diagnostic tests.[7]

Test	*Value*	*Interpretation*
Serum folate	<2 ng/mL	Diagnostic
	2–4 ng/mL	Measure methylmalonic acid and homocysteine levels
	>4 ng/mL	Normal
RBC/intraenterocyte folate	<165 µg/mL	Diagnostic
	165–190 µg/mL	Normal
Serum cobalamin	<200 pg/mL	Diagnostic
	200–300 pg/mL	Measure methylmalonic acid and homocysteine levels
	>300 pg/mL	Normal
Methylmalonic acid	70–270 mmol/L	Normal
Homocysteine	5–14 mmol/L	Normal

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Peripheral blood smear: Presence of macrocytes, hypersegmented neutrophils (>5% of neutrophils with 5 segments or >1% with 6 segments), anisocytosis (varying size of RBCs), giant polymorphs, and basophilic stippling. Few Howell–Jolly bodies and giant hypersegmented granulocytes can also be seen. There is varying degree of thrombocytopenia, leukopenia, and reticulocytopenia (reticulocyte count <1%). Peripheral smear usually reveals a picture of pancytopenia with suppression of all myeloid lineages. RBCs appear to be thicker and hyperchromic because of increased central pallor **(Figs. 1 and 2)**.[9]

Ineffective erythropoiesis cause intramedullary hemolysis leading to raised serum lactate dehydrogenase (LDH) and elevated indirect bilirubin. Haptoglobin levels can be reduced due to some amount of intravascular hemolysis.[9]

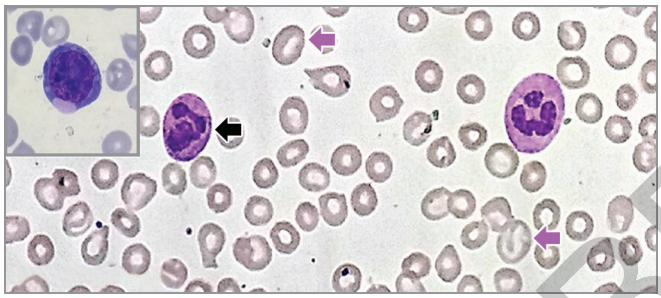


Fig. 1: Peripheral blood smear (40X): Hypersegmented neutrophil (black arrow), macro-ovalocytes (purple arrows); Inset: Megaloblast in a bone marrow aspirate smear.
Courtesy: Dr Harpreet Walia (Senior Consultant and Head), Department of Pathology, SGHS Hospital, Mohali, Punjab.

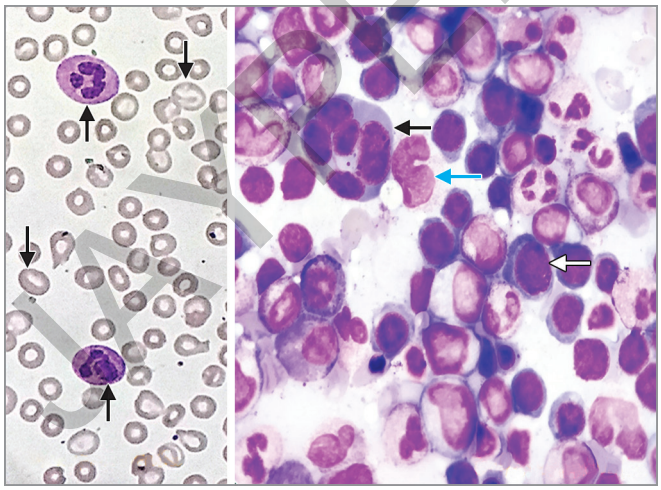


Fig. 2: Peripheral blood smear (40X): Hypersegmented neutrophils (upward arrows), macro-ovalocytes (downward arrows); Bone marrow aspirate smear (100X): Giant metamyelocyte (blue arrow), megaloblast (white arrow), and hypersegmented megakaryocyte (black arrow).
Courtesy: Dr Harpreet Walia (Senior Consultant and Head), Department of Pathology, SGHS Hospital, Mohali, Punjab.

Iron deficiency anemia is masked by folic acid and vitamin B_{12} deficiency as the synthesis of RBCs is reduced leading to raised serum iron, transferrin, and ferritin levels.

Bone marrow aspiration: Bone marrow aspiration (BMA) is routinely not indicated in all cases of megaloblastic anemia except when a diagnosis of refractory anemia, leukemia or myelodysplastic disease is suspected. Bone marrow appears hypercellular, erythroid series—the orthostatic erythroblasts are enlarged with nuclear cytoplasmic asynchrony. In the myeloid series megaloblasts manifest as large band cells.[7,9]

Effect of Folic Acid Deficiency on Pregnancy

As the pregnancy progresses the folate levels reduce to half as compared to the nonpregnant state. This is mainly due to hemodilution, increased renal clearance, and hormonal changes. During the latter half in the pregnancy the increased utilization by the developing fetus and the placenta and rapidly proliferating cells as well as increased catabolism of folic acid results in a negative feedback.

Deficiency of folic acid has been associated with spontaneous abortions, recurrent pregnancy loss, preterm delivery, abruptio placentae, pre-eclampsia, and growth restriction. High homocysteine levels can act as predictor for abruptio placentae and pre-eclampsia. Fewer studies have also linked folate deficiency to HELLP syndrome (hemolysis, elevated liver enzymes and low platelets).[8,10]

Effect of Folic Acid Deficiency Fetus and Neonate

Folic acid is has an essential role in the early embryonic development a deficiency during this period can lead to neural tube defect (NTD), heart defects and orofacial defects. As 50% of the pregnancies are unplanned, only 5–20% of the pregnant women start preconceptional folic acid. Preconceptional folic acid and supplementation during the pregnancy can reduce NTD by 72%. In low risk population who are planning to become pregnant or are not using any contraceptive method should start folic acid supplementation 30 days prior to conception in a dose of 400 µg (0.4 g) daily and continue this through the first trimester. In high risk women (history of NTD in previous pregnancies, partner affected by NTD, first-degree relative affected by NTD, prepregnancy diabetes mellitus, on antiepileptics-valproate and carbamazepine) should be given 4 g of synthetic folic acid.[11]

Fetal growth restriction, prematurity, low birth weight, and very low birth weight babies have been associated with maternal deficiency of folic acid.[10]

TREATMENT

Folic acid deficiency is treated by giving 5 mg of synthetic folic acid daily till 4 weeks postpartum. The reticulocyte

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count increases drastically within 4–7 days of starting treatment. Leukopenia and thrombocytopenia also gets corrected within days. The hemoglobin levels rises over a period of weeks. Iron supplementation should be started as soon as effective erythropoiesis starts. Hypersegmented neutrophils will persist for 10–14 days. Serum LDH levels and indirect bilirubin levels will normalize rapidly, a failure to fall may indicate iron deficiency anemia or error in diagnosis.

Vitamin B_{12} deficiency is mainly treated by parenteral therapy—1,000 µg daily for 1–2 weeks followed by weekly dose till hematocrit normalizes (6 weeks). Oral cobalamin (1,000–2,000 µg) can be given thereafter.[12]

Folic acid supplementation should not be started in megaloblastic anemia if cobalamin deficiency is not ruled out definitively. Treatment with folic acid will only correct the anemia and will worsen the neurological symptoms of cobalamine deficiency. Both folic acid and cobalamin should be given if vitamin B_{12} deficiency has not been ruled out.

In case of severe anemia blood transfusion should be given followed by parenteral therapy.

PREVENTION OF MEGALOBLASTIC ANEMIA

- Consume food rich in folic acid and vitamin B
- Do not overcook as these micronutrients are heat labile
- Use of fortified food, e.g., fortified wheat (folic acid, vitamin B, and iron)
- Folic acid prophylaxis

SUMMARY

Megaloblastic anemia is not an uncommon condition during pregnancy. Most of the cases are diagnosed in the latter half of the pregnancy when the demand of folic acid and vitamin B_{12} increases. High incidence is seen in multipara women and those with short interconceptional period. The most common cause of megaloblastic anemia is dietary deficiency. Folic acid prophylaxis should be started 30 days prior to planned conception; it effectively prevents NTD in the newborn. Megaloblastic anemia can be managed by pharmacotherapy however associated neurological symptoms may require a longer treatment and follow up.

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