INTRODUCTION

Folic acid is needed in higher doses in pregnancy because of the increased cell replication taking place in fetus, uterus and bone marrow. World Health Organization (WHO) recommends 800 μg folic acid per day. Preexisting deficiency is common in developing countries. It is mainly due to inadequate diet, intestinal malabsorption syndrome.

Vit B\textsubscript{12} is required for proper red blood cell formation, neurological functions and DNA synthesis. Recommended daily allowances (RDA) for vitamin B\textsubscript{12} in pregnancy is 2.6 μg per day. The main causes of vitamin B\textsubscript{12} deficiency include vitamin B\textsubscript{12} malabsorption from food, pernicious anemia, post-surgical cause, and dietary deficiency.

CASE REPORT

G2P1L1AO aging 24 years came with 8 months amenorrhea with a history of decreased appetite for 3 months, generalized weakness for 4 days, breathlessness for 4 days, swelling all over body for 4 days.

The patient had a report of Hb 6 g% at 20 weeks of gestational age for that patient had taken the treatment in the form of injectable iron only and when it dropped to 3 g%, the patient was referred to tertiary referral center by the treating hospital.

I advised the complete anemia profile, ANC profile and obstetric ultrasound.

• The reports were:
  - Hb: 3 g%, red blood cells (RBCs): 3.07 x 10\textsuperscript{12} cells/L, white blood cells (WBCs): 10.2 x 10\textsuperscript{9} cells/L, platelets: 33.2 x 10\textsuperscript{9} cells/L.
  - Ultrasound is suggestive of single live intrauterine pregnancy of 33.3 weeks gestation with cephalic presentation, AFI: 8–9 cm.

Obstetric Doppler: No significant abnormality in obstetric Doppler indices in the present scan.

Conclusion: Early intervention and diagnosis of megaloblastic anemia in late pregnancy reduce significant maternal and fetal morbidity and mortality.

Keywords: Folic acid, Megaloblastic anemia, Morbidity, Mortality, Pancytopenia, Vitamin B\textsubscript{12}.

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• Sr. Vitamin B<sub>12</sub>: 111.4 pg/mL
• Folic acid: 1 ng/mL
• Sr. Ferritin: 413.6 ng/mL
• Urine: Albumin-trace, pus cells–5–6/HPF, red cells–nil, epithelial cells–16–18/HPF

**Obstetric Ultrasound**

Thirty-two weeks, 4 days single live intrauterine pregnancy with cephalic presentation, BPD/HC and AC are less than 3 percentile suggestive of symmetrical intrauterine growth restriction, placenta found posterior, AFI 7–8 cm. Movements and cardiac activity regular.

**Obstetric Doppler**

There was a slightly raised S/D ratio in the midportion of the umbilical artery. Right uterine artery showed reduced PI. The flow pattern in rest vessels was normal.

**Ultrasound of Abdomen**

Within normal limits, patient admitted in intensive care unit for 2 days and treated with 3 units of PCV and parenteral administration of 3 doses of vitamin B<sub>12</sub> and vitamin C as per hematologist’s recommendation.

On D3 patient discharged with a platelet count of 41,000 cells/mm<sup>3</sup>, advised follow-up after 15 days for a complete blood count.

After 15 days reports were:
• Hb: 8.6 g%, PCV: 28.3 g%, RBCs: 3,07000 cells/mm<sup>3</sup>, WBCs: 10,200 cells/mm<sup>3</sup>,  
• Platelets: 3,32000 cells/mm<sup>3</sup> (Graph 2).

**Obstetric Ultrasound**

Single live intrauterine pregnancy of 33 weeks 3 days with cephalic presentation with a single loop of cord around the neck.

**Obstetric Color Doppler**

No significant abnormality in obstetric Doppler indices at present study.

**Treatment Modalities**

**Indications for Blood Transfusion**
• Severe anemia in later months of pregnancy.
• Refractory anemia.
• Quality and quantity: Fresh only packed cells 80–100 mL at a time.

**Advantages of PCV**
• Increased oxygen carrying capacity of the blood
• Hb may be utilized for the formation of new blood cells
• Stimulate erythropoiesis
• Improvement expected after 3 days.

**Treatment of vit B<sub>12</sub> Deficiency**
• Hydroxycobalamin<sup>4</sup> 1000 μg can be given IM to a total of 5.6 mg over the course of 3 weeks. 1000 μg is then necessary every 3 months for the rest of life.
It is now recommended that oral vitamin B₁² 2 mg/day is given as 1–2% of an oral dose is absorbed by diffusion, therefore, does not require intrinsic factor.

- A 2000 μg of oral vitamin B₁² daily, followed by a decreased daily dose of 1000 μg then 1000 μg weekly and finally monthly might be as effective as intramuscular administration.

**Treatment of Folate Deficiency**

Folate deficiency can be corrected by giving 5 mg of folic acid daily, treatment should be given for about 4 months to replace body stores, any underlying cause should be treated, prophylactic folic acid (400 μg daily) is recommended to reduce neural tube defects, women who have had a child with a neural tube defect should take 5 mg folic acid before and during a subsequent pregnancy.

**CLINICAL SIGNIFICANCE**

**Megaloblastic Anemia**

Megaloblastic anemia is anemia that results from inhibition of DNA synthesis during red blood cell production. When DNA synthesis is impaired, the cell cycle cannot progress from the G₂ growth stage to the mitosis (M) stage. Megaloblastic anemia is one of the acquired nutritional anemias that may complicate pregnancy. It is most often secondary to folate acid deficiency because folate requirements are increased.

**Folate Deficiency**

It mimics low levels of folic acid and derivatives in the body. Also known as vitamin B₁², folate is involved in adenosine, guanine, and thymidine synthesis. Anemia is late finding in folate deficiency. It is characterized by the appearance of large-sized, abnormal red blood cells (megaloblasts), which form when there are inadequate stores of folic acid within the body.

A deficiency of folate can occur when the body’s need for folate is increased when dietary intake or absorption of folate is inadequate, or when the body excretes more folate than usual. Medications like anticonvulsants, metformin, methotrexate, sulfasalazine, triamterene, birth control pills that interfere with the body’s ability to use folate may also increase the need for this vitamin. Research indicates that exposure to ultraviolet light, including the use of tanning beds, can lead to folate deficiency. The deficiency is more common in pregnant women, infants, children, and adolescents.

A defect in homocysteine methyltransferase or a deficiency of B₁² may lead to a so-called “methyl trap” tetrahydrofolate (THF), in which THF is converted to a reservoir of methyl-THF which thereafter has no way of being metabolized, and serves as a sink of THF that causes a subsequent deficiency of folate. Thus, a deficiency in vitamin B₁² can generate a large pool of methyl-THF that is unable to undergo reactions and will mimic folate deficiency.

Folate deficiency during gestation or infancy due to development by the fetus or infant of autoantibodies to the folate receptor might result in various developmental disorders including autism spectrum disorders. Studies suggest that insufficient folate and vitamin B₁² status may contribute to major depressive disorder and that supplementation might be useful in this condition. The role of vitamin B₁² and folate in depression is due to their role in transmethylation reactions, which are crucial for the formation of neurotransmitters (e.g., serotonin, epinephrine, purines, nicotinamides, phospholipids) The proposed mechanism, is that low levels of folate or vitamin B₁² can disrupt transmethylation reaction, leading to an accumulation of homocysteine (hyperhomocysteinemia) and to impaired metabolism of neurotransmitters (especially the hydroxylation of dopamine and serotonin from tyrosine and tryptophan) phospholipids, myelin, and receptors. High homocysteine levels in the blood can lead to vascular injuries by oxidative mechanisms which can contribute to cerebral dysfunction. All of these can lead to the development of various disorders, including depression.

Vitamin B₁² exists in several forms and contains the mineral cobalt, so compounds with vitamin B₁² activity are collectively called “cobalamins”. Methylcobalamin is the forms of vitamin B₁² that are active in human metabolism. Vitamin B₁² functions as a cofactor for methionine synthase and L-methylmalonyl-CoA mutase. Methionine synthase catalyzes the conversion of homocysteine to methionine. Methionine is required for the formation of S-adenosylmethionine, a universal methyl donor for almost 100 different substrates, including DNA, RNA, hormones, proteins, and lipids. L-methylmalonyl-CoA mutase converts L-methylmalonyl-CoA to succinyl-CoA in the degradation of propionate, an essential biochemical reaction in fat and protein metabolism. Succinyl-CoA is also required for hemoglobin synthesis.

Vitamin B₁² deficiency is an independent risk factor for fetal neural tube defects. The underlying mechanisms involve the homocysteine pathway by elevation in plasma homocysteine.

**Vitamin B₁² Deficiency**

Pathological changes that occur due to B₁² deficiency are demyelination, axonal degeneration, neuronal death elevation in homocysteine, reduced tetrafolate as well
as the secondary elevation of guanidinoacetate may be involved in the pathogenesis of encephalopathy. This deficiency has also been associated with recurrent fetal loss and neonatal death. Bennet found that severe deficiency caused a high incidence of recurrent fetal loss. The cause of this recurrent fetal loss is two-fold. It is due to damage to decidua and chorial vessels leading to abnormal placentation and secondary because of direct embryotoxicity from hyperhomocysteinemia, can cause anencephaly, this may be due to the vitamin B₁² is involved in the metabolism of neural tissue.

**Pancytopenia**

It is the simultaneous presence of anemia, leukopenia, and thrombocytopenia. The underlying mechanism is decreased in hemopoietic cells production, marrow replacement by abnormal cells, suppression of marrow growth and differentiation, ineffective hematopoeisis with cell death, defective cell formation which are removed from circulation, antibody-mediated sequestration or destruction of cells and trapping of cells in a hypertrophied and overactive reticuloendothelial system.

Megaloblastic anemia as a cause of pancytopenia falls in the wide range of results reported in local studies vary from 38 to 72%.

**Folic Acid and Vitamin B₁²**

Large amounts of folic acid can mask the damaging effects of vitamin B₁² deficiency by correcting the megaloblastic anemia caused by vitamin B₁² deficiency without correcting the neurological damage that also occurs. Preliminary evidence suggests that high serum folate levels might not only mask vitamin B₁² deficiency, but could also exacerbate the anemia and worsen the cognitive symptoms associated with vitamin B₁² deficiency. Permanent nerve damage can occur if vitamin B₁² deficiency is not treated. For these reasons, folic acid intake from fortified food and supplements should not exceed 1,000 μg daily in healthy adults.

**Complications of Severe Anemia**

**During Pregnancy**
- Preeclampsia
- Intercurrent infection
- Heart failure
- Preterm labor

**During Labor**
- Uterine inertia
- Postpartum hemorrhage
- Cardiac failure
- Shock.

**During Puerperium**
- Subinvolution
- Failing lactation
- Pulmonary embolism.

**Risk Periods During Pregnancy with Severe Anemia**
- At about 30–32 weeks of pregnancy.
- During labor.
- Immediate following delivery.
- Any time in puerperium especially 7 to 10 days following delivery.

**Differential Diagnosis**

Many rare cases of megaloblastic anemia (unrelated to vitamin deficiency) have been identified including rare enzyme deficiencies known as inborn errors of metabolism and primary bone disorder including myelodysplastic syndromes and acute myeloid leukemia.

**CONCLUSION**

Early intervention and diagnosis of megaloblastic anemia in late pregnancy reduce significant maternal and fetal morbidity and mortality.

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