Severe Pancytopenia in Pregnancy Secondary to Megaloblastic Anemia: Report of Two Cases

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Received: 22 June 2024

Accepted: 30 July 2024

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DOI 10.5001/omj.2027.13

Abstract

Megaloblastic anemia is the second most common cause of anemia in pregnancy after iron deficiency anemia. If severe, it can lead to bone marrow suppression leading to pancytopenia. This can have maternal as well as fetal complications due to lack of oxygen carrying capacity by maternal red blood cells and altered placental function. It is important to ascertain the cause of anemia before giving any form of parenteral therapy for its correction. We present here two rare cases of sudden onset severe pancytopenia in pregnancy and the diagnostic dilemma faced during their workup. Both the antenatal women presented in third trimester with pancytopenia and showed a marked improvement within 10-15 days of treatment with parenteral B12 injections and had a good perinatal outcome.

Keywords: Pancytopenia; Megaloblastic; Anemia; Pregnancy.

Introduction

Anemia in pregnancy is defined as hemoglobin values less than 11 gm/dL and severe anemia is defined as hemoglobin values less than 7 gm/dL and very severe anemia as values less than 4 gm/dL.[1-3] The prevalence of megaloblastic anemia in pregnancy is reported to be 28-40%.[4,5] In women with reduced dietary intake especially vegetarian diet, sudden increase in dietary demands in third trimester leads to sudden fall in hemoglobin levels.[6] Vitamin B12 helps in formation of DNA which is essential for cell multiplication for fetal development. Hyperhomocytinemia secondary to vitamin B12 deficiency can affect fetal growth.[7,8] An Indian study done in women with severe anemia shows that maternal and fetal complications are more in megaloblastic anemia than iron deficiency anemia.[5] There are few similar cases reported in the literature, where antenatal women had presented with severe anemia at later gestation.[9-12] All these cases presented at a later period of gestation at around 30 weeks with hemoglobin values of 3.7-6.4 gm/dL and responded very well to parenteral B12 injections. In all the cases, a significant rise in hemoglobin value was seen over 10-15 days. The present two cases also add data to the literature about the clinical presentation, diagnostic dilemma and workup of severe pancytopenia in pregnancy.

Case Report

Case one

A 25 years old primigravida, strict vegetarian by diet, presented at 31 weeks with easy fatiguability and breathlessness since 1 month, jaundice, and fever since 10 days. There was no history of nausea, vomiting or any antepartum haemorrhage. She had a Hb of 5.0 gm/dL one month before admission but didn't take any treatment. She didn't have any neurological symptoms. At the time of admission, she had a pulse rate of 100/minute, blood pressure of 110/70 mmHg, temperature of 100-degree F, respiratory rate of 22 per minute, and saturation of 92%

on room air. She had severe pallor (figure 1), mild icterus, anasarca, and bilateral basal crept on examination. There was no angular stomatitis, cheilosis or glossitis. On investigations, she had pancytopenia with hemoglobin of 1.8 gm/dL (table 1) and the cause was found to be megaloblastic anemia secondary to vitamin B12 deficiency (table 2). The uterine height was corresponding to the period of gestation and there was no free fluid. The uterus was relaxed and there was no abdominal tenderness. Ultrasound abdomen ruled out antepartum haemorrhage or any hemoperitoneum which can lead to sudden fall in hemoglobin in pregnancy. She was given a total of four units of packed red cell transfusions along with intravenous B12 in a dose of 2500 mcg total three doses on alternate days (day 0,2,4) followed by weekly injection for 9 weeks . Her platelet and leucocyte count increased rapidly while Hb showed a slow rise (table 3). She went into preterm labor on the 7th day of treatment and injection Magnesium sulphate, Betamethasone and oral Nifedipine was started for neuroprotection, lung maturity and tocolysis respectively. She delivered a 1.35 Kg baby after 18 hours of this treatment and baby was shifted to NICU in view of low birth weight. At birth, baby's hemoglobin was 18 gm/dL and he gained weight over one month stay in NICU and was discharged at a weight of 1.8 Kg. The mother continued oral iron and B12 supplementation for another six months. After three months of delivery, her hemoglobin value was 10.8 gm/dL and a normal platelet count of 3.8 lakh /dL.

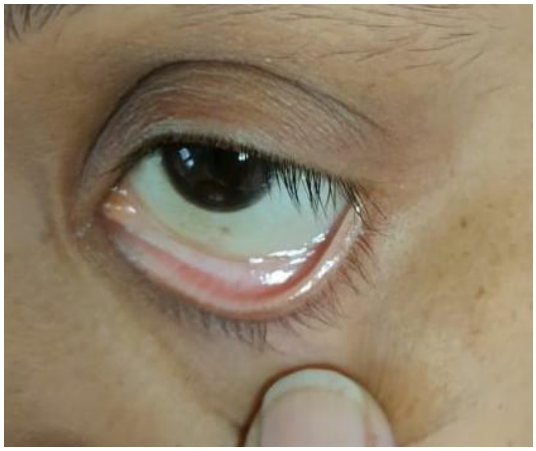

Figure 1: Pallor in palpebral conjunctiva.

Table 1: On admission.

	Case 1	**Case 2**
Hemoglobin (11.5-16 gm/dL)	1.8	2.0
Hematocrit (40-50%)	5.4	5.7
RBC count (4.5-5.5 million)	1.08	0.58
MCV (83-100 fL)	98	101
MCH (27-32 pg)	31.0	34.7
MCHC (31.5-34.5 gm/dL)	34.2	34.9
Red cell distribution width (11-16%)	20.7	22.8
TLC (4,000-10,000 /dL)	2,540	1,750
DLC	N51/L47/M1/E1	N43/L56/M1/E0
Platelet count (1.5-4.5 lakh/dL)	11,0000	9,000
Immature platelet fraction (0.64-6.04%)	5.4%	4.8%
Reticulocyte count (0.5-2.5%)	0.4%	0.2%
INR	1.0	1.0

	Case 1	Case 2
Peripheral smear	Macrocytic normochromic RBCs with anisopoikilocytosis, target cells+, macroovalocytes and 3 nucleated RBC/100 WBC, Hypersegmented neutrophils ++ (figure 2), platelet grossly reduced, few large platelets	Macrocytic normochromic RBCs (figure 3), 5 nucleated RBC/100 WBC with macroovalocytes, Hypersegmented neutrophils ++, platelet grossly reduced, few large platelets
Bone marrow aspirate	Erythroid hyperplasia with megaloblastic maturation Myeloid and megakaryocytic series showed adequate maturation. Prussian blue stain showed adequate iron stores (grade 3+)	Erythroid hyperplasia with megaloblastic maturation Myeloid and megakaryocytic series showed adequate maturation. Prussian blue stain showed adequate iron stores (grade 2+)

Table 2: Investigations done to reach the diagnosis and underlying cause.

	Case 1	Case 2
Serum B12 (197-771 pg/mL)	76	68
Serum Folate (3-12 ng/mL)	2.5	1.8
Serum Ferritin (30-400 ng/mL)	>1000	>1000
Serum Iron (33-193 mcg/dL)	295	415
TIBC (228-428 mcg/dL)	344	464
Serum LDH (135-214 U/L)	1559	1227
Serum Bilirubin (0.2-1.2 mg/dL)	8.58	1.4
Indirect Bilirubin (0.2-0.9 mg/dL)	2.16	0.89
Direct Bilirubin (0.0-0.3 mg/dL)	6.42	0.51
ALT (0-45 U/L)	58	40
AST (0-45 U/L)	121	123
Serum creatinine (0.6-1.3 mg/dL)	0.4	1.2
Serum TSH (0.27-4.2 mIU/mL)	3.68	1.70
Sickling test	Negative	Negative
HPLC	96.3	96.4
HbA	3.2	3.2
HbA2	0.5	0.4
HbF		
Direct Coomb's test	Negative	Negative
Antinuclear antibody	Negative	Negative
Fundus examination	Anemic retinopathy	Anemic retinopathy
HIV	Negative	Negative
HbsAg	Negative	Negative
HCV	Negative	Negative

Case two

A 28-year-old second gravida, strict vegetarian by diet, presented at 28 weeks of pregnancy with breathlessness and palpitations along with cough since 1 month. There was neither associated pedal edema, jaundice, easy bruisability, nor history of prior blood transfusion. She didn't have any pain in the abdomen or any antepartum haemorrhage. There was a history of infrequent intake of oral iron and folate supplements. Based on her Hb levels and poor compliance to oral iron, she was given 6 doses of intravenous Iron sucrose 200 mg on alternate days at a private hospital, following which her Hb fell to 5.4 gm/dL over 15 days and further to 2.0 gm/dL over one month after treatment. However, her serum Ferritin levels were not done before this. At the time of presentation, she had a pulse rate of 108 /minute, blood pressure of 120/80 mmHg, respiratory rate of 16 per minute, and oxygen saturation of 96% on room air and had severe pallor. Blood investigations showed in table 1 & 2 suggested final diagnosis of megaloblastic anemia. There was no angular stomatitis, cheilosis or glossitis.There was no evidence of abruptio placenta or spontaneous hemoperitoneum on abdominal ultrasound. She was given four units of packed red blood cell over four days. She was also given intravenous B12 (Methylcobalamin) in a dose of 2500 mcg total three doses on alternate days (day 0,2,4) followed by weekly injection for 9 weeks . She underwent elective cesarean section at 38 weeks under spinal anesthesia in view of previous cesarean section with breech presentation and delivered a 2.5 Kg healthy baby. The intraoperative blood loss was estimated as 600 mL. The mother and baby were discharged in good health on postoperative day 4. She continued oral iron and B12 supplementation for another six months. After three months of delivery, her hemoglobin value was 11.0 gm/dL and platelet count of 3.2 lakh/dL.

Different diagnosis

The various causes of sudden onset of pancytopenia are

1. HELLP syndrome: Our cases didn't have any high blood pressure records or any features of pre-eclampsia

2. Antepartum haemorrhage: The history, examination and abdominal ultrasound were done to rule out abruptio placenta and there was no placenta previa

3. Spontaneous hemoperitoneum: History and examination didn't suggest any clinical feature of hemoperitoneum or any features of DIC.

4. Autoimmune disorders: ANA and DCT were negative for both the patients

5. Bone marrow disorders: Bone marrow aspiration was done

6. Viral infections: HIV, HBsAg and HCV were negative for both the patients

Initially, we gave packed red cell transfusion to increase the oxygen carrying capacity followed by parenteral B12 supplementation in form of alternate day therapy for three doses of intravenous injection of combined 2500 mcg cobalamin with 0.7 mg folic acid and 12 mg of Niacinamide available in a single vial. These three doses were given on day 0,2 and 4 followed by weekly nine injections of same dose. Since the patient showed a good response to the treatment, it was changed to oral 1500 mcg mecobolamin daily tablet along with the routine iron folate prophylaxis. The response to the treatment is shown in Table 3.

Table 3: Follow up on treatment.

	On admission		**After blood transfusions**		**After 3 doses of B12 injections**		**After 6 doses of B12**		**After 12 doses of B12**	
	Case 1	**Case 2**	**Case 1**	**Case 2**	**Case 1**	**Case 2**	**Case 1**	**Case 2**	**Case 1**	**Case 2**
Hb (gm/dL)	1.8	2	3.4	5.2	6.6	7.5	6.7	8.4	9	9.2
MCV (fL)	98	101	90	93	85.4	88.5	85.6	86.5	82.5	83.6
TLC (counts/dL)	2,540	1,750	3,400	2,000	5,590	5,490	10,860	6,800	11,460	10,980

Platelet(counts/dL)	11,000	9,000	12,000	7,000	18,000	16,000	1,80,000	62,300	2,20,000	4,80,640
Reticulocyte count (%)	0.40%	0.20%	-	-	0.80%	1.30%	9.80%	12.60%	-	-
Total Bilirubin (mg/dL)	8.58	1.4	-	-	3.2	0.8	1.02	-	-	-

Discussion

As per the National Family Health Survey-5, 52% of pregnant women in India have anemia.[13] The increased demand for nutrients during pregnancy can't be met by a vegan or lacto-vegetarian diet which lacks vitamin B12 and folate and hence leads to megaloblastic anemia. In deficiency of vitamin B12 or folate, nuclear maturation lags behind cytoplasmic maturation leading to ineffective erythropoiesis. The deficiency can lead to loss of appetite and weight, weakness, headache, palpitations, neurological symptoms and psychiatric symptoms.[14] In India, the prevalence of macrocytic anemia in pregnancy can be as high as 40%.[5] Iron deficiency being much more common than B12 deficiency is usually presumptive diagnosis in pregnant females.[15] The administration of intravenous iron sucrose without establishing the cause led to the worsening of anemia in the second case, as the red blood cells are pushed toward erythropoiesis but was ineffective.

The incidence of maternal and perinatal complications are more than those seen in iron deficiency anemia. These include risk of preterm birth,[16] risk of NTDs, pregnancy losses, gestational diabetes, pre-eclampsia, lower birth weight.[17] Thus, it is important to recognise this condition early in pregnancy and treat it to avoid these complications. However, its diagnosis can be challenging during pregnancy due to its varied presentation like severe pancytopenia[9-12] or mimicking HELLP syndrome[18] or as pyrexia with anemia.[19] There are few similar cases reported previously including one twin gestation with presentation in third trimester in all the cases. The hemoglobin values in these cases ranged from 3.7 gm/dL to 6.4 gm/dL.[9-12] All these cases presented as pancytopenia in pregnancy. Serum vitamin B12 levels were reduced in two cases and in rest two cases the diagnosis was based on MCV and peripheral smear picture. All these patients responded well to the parenteral B12 injections and their hemoglobin improved significantly over 10-15 days.[9-12]

There is no single gold standard test for diagnosis. Instead, we must use a combination of investigations like serum vitamin B12 and folate levels and peripheral smear to diagnose megaloblastic anemia, as shown in figure 2 and 3. In case of any unusual clinical finding bone marrow should be done to check for megaloblastic erythroid hyperplasia with preserved trilineage hematopoieisis.[20] Treatment of megaloblastic anemia compromises of oral or intravenous administration of folic acid and vitamin B12. Asymptomatic patients can be given oral therapy and symptomatic ones need intravenous therapy. The therapy with vitamin B12 and folic acid does not cure anemia promptly so patients having severe anemia or symptomatic patients need blood transfusion.[21] After appropriate treatment, hemoglobin usually starts rising within a week and comes to normal levels in 4-8 weeks.

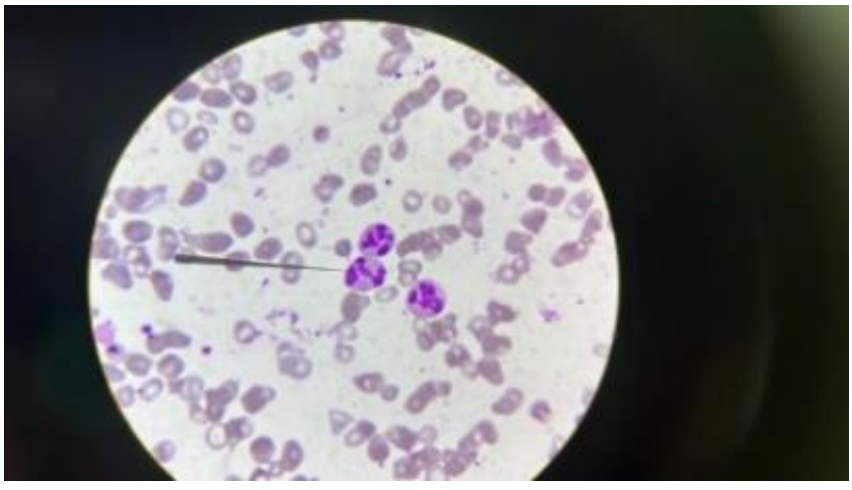

Figure 2: Hypersegmented neutrophils.

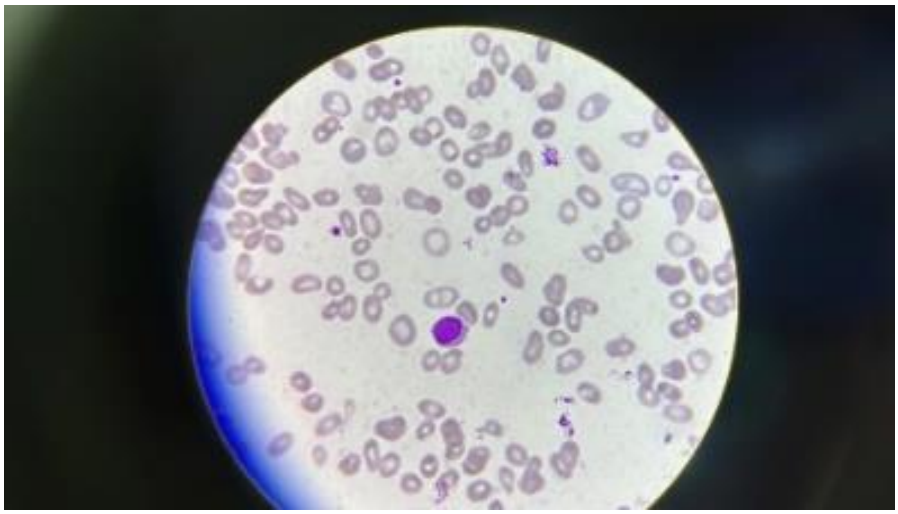

Figure 3: Macrocytic RBC.

Conclusion

In complete diagnostic workup of pancytopenia during pregnancy, megaloblastic anemia should be considered as one of the cause. Diagnosis is based on MCV, appearance of megaloblast on peripheral smear and serum vitamin B12 levels. It responds very well to parenteral supplementation of vitamin B12 and thus must be identified timely.

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