ORIGINAL RESEARCH

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Pancytopenia in Obstetric Inpatients at Karnataka Institute of Medical Sciences, Hubli-Etiological Considerations

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ABSTRACT Objective: Pancytopenia refers to the combination of anemia, leukopenia, and thrombocytopenia. Special interest has been directed to pancytopenia in obstetric population as an increasing incidence was observed in the geographical location of the population under study. **Material and Methods:** It's a prospective, observational study done over a period of 18 months at Karnataka Institute of Medical Sciences (KIMS), Hubli. Obstetric in-patients (antenatal and postnatal cases up to 42 days postpartum) admitted with a diagnosis of pancytopenia were included. A thorough history, clinical examination, and laboratory evaluation including serum vitamin B_{12} and serum folic acid levels were carried out. They were followed for feto-maternal outcome. **Results:** The incidence of maternal pancytopenia in our study was 0.45%. This study observed that most of the participants were vegetarian by diet with vitamin B_{12} deficiency followed by folate deficiency leading to pancytopenia, with majority (37.7%) hailing from Gadag district. 91.1% of the patients with pancytopenia were found to have vitamin B_{12} deficiency and 62.2% among them had serum vitamin B_{12} levels as low as 50-100 pg/mL. Most of the patients [11 (24.44%)] had serum folic acid levels between 4.1-5.0 ng/mL. **Conclusion:** Association of pancytopenia with pregnancy is a rare entity, yet it has increased the risk of poor maternal and fetal outcome. Proper dietary counselling and well-balanced dietary plans can prevent the micronutrients deficiency and avoid the deleterious consequences like pancytopenia.

Keywords: Pancytopenia; pregnancy; vitamin B_{12}; folic acid

The simultaneous occurrence of anaemia, leukopenia, and thrombocytopenia is known as pancytopenia, which is defined as a reduction in all three major cellular constituents of blood.[1] World Health Organization definition of anaemia is haemoglobin of less than 11 g/dL in females. Leukopenia is defined as white blood cell (WBC) count of less than 4×10^9/L and platelet count of less than 150×10^9/L is referred to as thrombocytopenia. Therefore, rather than being a single disease, the triad of findings could be the consequence of many disease processes that either directly or indirectly affect the bone marrow.[2]

It is a common feature of many severe and sometimes fatal illnesses and can be caused by various conditions, ranging from leukaemia and simple drug-induced bone marrow hypoplasia and megaloblastic anaemia to dangerous aplastic anaemia. However, aetiology of pancytopenia varies from one geographical region to another.[3] Therefore, the objective of this study was to study the prevalence of pancytopenia in obstetric population at Karnataka Institute of Medical Sciences (KIMS) Hubli and etiopathology of pancytopenia in obstetric population.

Pregnancy is a state of high metabolic demand. Pregnant women commonly have anaemia and thrombocytopenia, which are typically caused by the usual dilutional impact of increased plasma volume during pregnancy, but they are rarely severe enough to necessitate intervention unless made worse by defi-

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ciency of micronutrients. In developing nations, anaemia linked to nutritional deficiencies is common.[1]

Special interest has been directed to pancytopenia in obstetric population as an increasing number of antenatal and postnatal cases with pancytopenia was observed in the geographical location of the population under study, that is the obstetrics in-patients presenting to KIMS, Hubli.

MATERIAL AND METHODS

It is a prospective, observational, non-comparative, non-randomized, analytical study. Duration of the study was 18 months, after ethical committee clearance. Permission was obtained from Karnataka Institute of Medical Sciences Ethics Committee (date: January 22, 2021, no: 412: 2020-21) prior to the study. The study was done in accordance with the Helsinki Declaration principles. Total of 45 women with pancytopenia were studied. All obstetric patients admitted to KIMS, Hubli, with a diagnosis of pancytopenia with haemoglobin of less than 11 g/dL, WBC count of less than 4×10^9/L and platelet count of less than 150×10^9/L were included in the study. In all patients, after an informed consent, detailed history with emphasis on symptoms of anemia, history of infections and bleeding tendencies, detailed menstrual history, history of postpartum hemorrhage, history of blood transfusions, and diet history was taken. Complete physical examination with emphasis on lymphadenopathy, hepatosplenomegaly, nail changes, tongue changes, pigmentation, and gum hypertrophy were done. Basic blood tests such as complete haemogram, peripheral smear, reticulocyte count, liver function tests, renal function tests, and serology for human immunodeficiency virus and HBsAg were done in all patients. Coronavirus disease-2019 (COVID-19) Rapid Antigen Test was done in all patients. Vitamin B_{12} assay and folic acid levels were done in all patients. Additional investigations for malaria, dengue, antinuclear antibody (ANA), cytomegalovirus, Epstein Barr virus were done when deemed necessary to arrive at the cause of pancytopenia when other previously mentioned test results were not conclusive. Bone marrow examination was done on patients where diagnosis could not be achieved and who do not respond to initial therapy guided by above investigations.

INCLUSION CRITERIA

Obstetric in-patients (antenatal cases and postnatal cases up to 42 days postpartum) admitted in the hospital with a diagnosis of pancytopenia with haemoglobin of less than 11 g/dL, WBC count of less than 4×10^9/L and platelet count of less than 150×10^9/L.[2]

EXCLUSION CRITERIA

i. Patients with a history of malignancy.

ii. Patients receiving chemotherapy and patients receiving radiotherapy were excluded from the study.

The inclusion and exclusion criteria have been elaborated in a flowchart in Figure 1.

STATISTICAL ANALYSIS

All the data collected were tabulated & analysed. For continuous variables, mean +/- standard deviation were used for categorical data, number (n) and percentage (%) were used in data summaries and diagrammatic representations. These data were used for statistical analysis by SPSS V23.0 (IBM, USA) software and Microsoft Office 365 (Microsoft, USA).

RESULTS

The present study was carried out on all obstetric inpatients admitted with a diagnosis of pancytopenia with haemoglobin of less than 11 g/dL, WBC count of less than 4×10^9/L, and platelet count of less than 150×10^9/L in the Department of Obstetrics and Gynaecology, Karnataka Institute of Medical Sciences, Hubballi for a period of 18 months between 1st February 2021 and 31st September 2022.

1. In the present study, total number of obstetric inpatients during the study period was 9,800. Total number of obstetric patients with pancytopenia was 45. The prevalence of pancytopenia in obstetric patients was 0.45%.

2. Out of the 45 patients with pancytopenia, 13 patients (28.89%) were in the age group of 20-21 years. Ten (22.22%) patients were in the age group of 22-23 years. Ten (22.22%) patients were in the age group of 24-25. Nine (20%) patients were in the age group of 26-27 years and 3 (6.67%) patients were in the

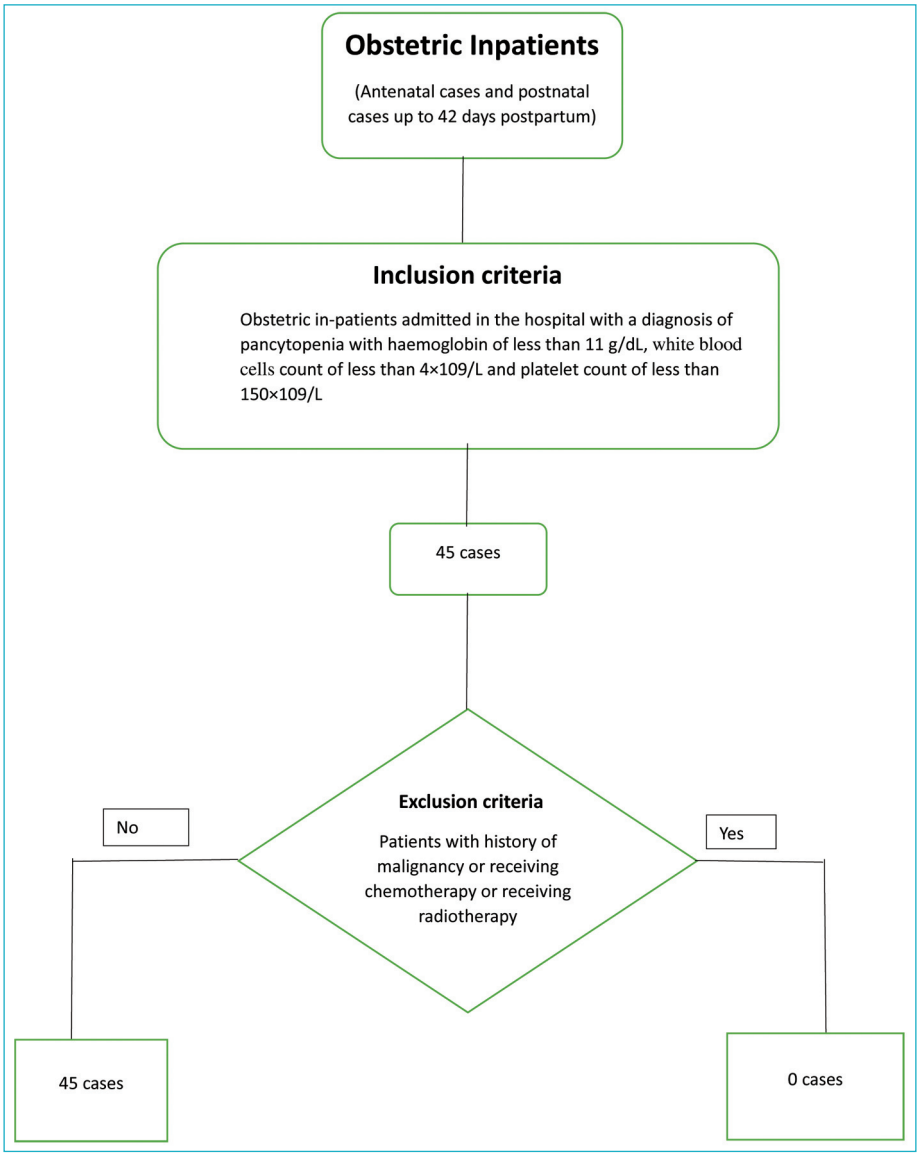

FIGURE 1: Showing the flowchart of inclusion and exclusion criteria of the study.

age group of more than 28 years. Mean age was 24.49 and standard deviation was found to be 2.76.

3. In this study, out of the 45 patients with pancytopenia, 1 patient (2.22%) was <28 weeks gestational age at admission, 6 patients (13.33%) between 28-32 weeks, 11 patients (24.44%) between 32-36 weeks, and 24 patients (53.33%) presented between 36 weeks to 40 weeks. Three patients were postnatal at admission. Mean gestational age was 35.45 weeks with a standard deviation of 3.58.
4. In this study, out of the 45 patients with pancytopenia, 27 patients (60%) had a vegetarian diet and 18 patients (40%) had a mixed diet.
5. Table 1 shows the distribution of cases based on clinical symptoms at presentation, 44 patients (97.78%) presented with fatigue, 23 patients (51.11%) presented with tingling and numbness, 16 patients (35.56%) presented with swelling of lower limbs, 10 patients (22.22%) presented with dyspnoea and fever each. Eight patients (17.78%) presented with bleeding tendencies, 4 patients (8.88%) pre-

TABLE 1: Distribution of cases based on clinical symptoms at presentation.

Symptoms	No of patients (n)	% of patients (n/45)
Fatigue	44	97.78
Tingling and numbness	23	51.11
Giddiness	19	42.22
Swelling of lower limbs	16	35.56
Others	13	28.89
Dyspnoea	10	22.22
Fever	10	22.22
Bleeding tendencies	8	17.78
Imminent symptoms	4	8.88

TABLE 2: Distribution of cases based on Hb levels (g/dL), TLC (cells/mm^3) and platelet count (cells/mm^3) at admission.

a. Distribution of cases based on Hb levels (g/dL) at admission		
Levels of Hb (g/dL) at admission	No of patients (n)	% of patients (n/45)
<4.9 g/dL	14	31.11
5-7.9 g/dL	30	66.67
8-10.9 g/dL	1	2.22
Total	45	100.00
Mean	5.62	
Standard deviation	1.22	
b. Distribution of cases based on TLC (cells/mm^3) at admission		
Levels of TLC (cells/mm^3) at admission	No of patients (n)	% of patients (n/45)
<500	1	2.22
501-1,000	9	20.00
1,001-2,000	12	26.66
2,001-3,999	23	51.11
Total	45	100.00
Mean	2742	
Standard deviation	849.2	
c. Distribution of cases based on platelet count (cells/mm^3) at admission		
Levels of platelets (cells/mm^3)	No of patients (n)	% of patients (n/45)
<19.9 k	9	20.00
20-39.9 k	8	17.78
40-59.9 k	8	17.78
60-79.9 k	9	20.00
>=80 k	11	24.44
Total	45	100.00
Mean	51.35	
Standard deviation	30.62	

Hb: Haemoglobin; TLC: Total leukocyte count.

sented with imminent symptoms such as headache, blurring of vision, vomiting, epigastric pain. Thirteen patients (28.89%) presented with other symptoms such as leaking per vagina, bleeding per vagina, pain abdomen or decreased foetal movements.

6. Table 2 shows the distribution of cases based on haemoglobin levels (g/dL), total leukocyte count (cells/mm^3) and platelet count (cells/mm^3) at admission. Mean haemoglobin level was 5.62 g/dL and standard deviation was found to be 1.22. Mean total leukocyte count was 2,742 cells/mm^3 with a standard deviation of 849.2. Mean platelet count was 51.35 k cells/mm^3 with a standard deviation of 30.62 k.
7. Nineteen patients (42.22%) had peripheral smear showing dimorphic anaemia followed by megaloblastic anaemia in 18 patients (40%). In 5 patients (11.11%), peripheral smear showed microcytic hypochromic anaemia and normocytic normochromic anaemia in 3 patients (6.67%).
8. Table 3 shows the distribution of cases based on serum vitamin B_{12} levels (pg/mL). Normal serum vitamin B_{12} levels are between 197-771 pg/mL. Twenty eight patients (62.22%) had serum vitamin B_{12} levels as low as between 51-100 pg/mL. The levels of serum vitamin B_{12} were <50 pg/mL in 6 patients (13.33%), 101-150 pg/mL in 5 patients (11.11%), and >151 pg/mL in 5 patients (11.11%). Thus, in this study, 41 patients (91.11%) had vitamin B_{12} deficiency, and three patients had normal serum vitamin B_{12} levels. It could not be assessed in one patient due to early mortality. Mean serum vitamin B_{12} levels was 92.87 pg/mL with a standard deviation of 43.2.
9. Table 4 shows the distribution of cases based on serum folic acid levels (ng/mL).

TABLE 3: Distribution of cases based on serum vitamin B_{12} levels (pg/mL).

Serum vitamin B_{12} (pg/mL)	No of patients (n)	% of patients (n/45)
</=50	6	13.33
51-100	28	62.22
101-150	5	11.11
>=151	5	11.11
Could not be done (mortality)	1	2.22
Total	45	100.00
Mean	92.87	
Standard deviation	43.20	

TABLE 4: Distribution of cases based on serum folic acid levels (ng/mL).

Serum folic acid (ng/mL)	No of patients (n)	% of patients (n/45)
<=2.0 ng/mL	10	22.22
2.1-3.0 ng/mL	3	6.67
3.1-4.0 ng/mL	7	15.56
4.1-5.0 ng/mL	11	24.44
5.1-6.0 ng/mL	9	20.00
>=6.1 ng/mL	4	8.89
Could not be done (mortality)	1	2.22
Total	44	97.78
Mean	3.85	
Standard deviation	2.08	

TABLE 5: Etiology of pancytopenia in our clinical setting.

Etiology	Number of patients
Vitamin B_{12} and folic acid deficiency	41
Pneumonia with sepsis (both COVID positive)	2
Dengue	2
Enteric fever	4
Systemic lupus erythematosus	1
Chronic liver disease	1

Normal serum folic acid levels are between 1.72 and 17.24 ng/mL. Most of the patients (11 in number, 24.44%) had serum folic acid levels between 4.1-5.0 ng/mL. The levels of serum folic acid were <2 ng/mL in 10 patients (22.22%), 2.1-3.0 ng/mL in 3 patients (6.67%), 3.1-4.0 ng/mL in 7 patients (15.56%), 5.1-6.0 ng/mL in 9 patients (20.00%), >6.1 ng/mL in 4 patients (8.89%). Could not be assessed in one patient due to early mortality. Mean serum folic acid level was 3.85 ng/mL with a standard deviation of 2.08.

10. Dengue and Widal tests were done in 10 patients who presented with fever. Out of which Dengue was positive in 2 patients and Widal was positive in 4 patients. ANA profile was done in 3 patients to rule out autoimmune aetiology, out of which 1 patient had a positive test result with anti-smith and anti-ribonucleoprotein antibodies suggestive of systemic lupus erythematosus.

11. Bone marrow examination was done on patients where diagnosis could not be achieved and who do not respond to initial therapy guided by above investigations. Results of bone marrow examination carried out in 2 patients are as follows:

    a. Combined normoblastic and myeloblastic erythroid hypercellular marrow

    b. Combined normoblastic and megaloblastic erythroid hypercellular marrow

ETIOLOGY OF PANCYTOPENIA IN OBSTETRIC PATIENTS IN OUR STUDY

Based on the clinical presentation and the investigations carried out, the various conditions leading to pancytopenia in obstetric patients in our clinical setting are described in Table 5. Majority of patients (41 in number, 91.11%) had vitamin B_{12} and folic acid deficiency leading to pancytopenia. Some of them had solely vitamin B_{12} and folic acid deficiency and some in association with other causes such as pneumonia (COVID positive), dengue, enteric fever, SLE, and chronic liver disease. Patients showed clinical improvement witnessed by improvement in symptoms and well-being with vitamin B_{12} and folic acid supplementation.

DISCUSSION

Pancytopenia in obstetrics patients, although a rare presentation, can be challenging for the clinician in terms of diagnosis and management. The purpose of the study was to find the etiopathology, to arrive at the treatable causes and understand the approach to the management. Results were analysed and evaluated with standard literature. In this study, 45 women (0.45%) out of 9,800 were found to have pancytopenia. As compared to an observational study carried out in Bijapur by Mathapati et al., where 38 women out of 1,230 patients (3% incidence) were found to have pancytopenia and 50 patients out of 1,550 (3.22% incidence) were found to have pancytopenia in another cross-sectional observational study in Haryana by Nath and Sheth.[1,4]

In our study, 60% of the patients were vegetarian by diet, as compared to study by Mathapati et al.

and Nath and Sheth, where all the participants enrolled in the study were vegetarian in diet.[1,4]

The mean haemoglobin in the present study was 5.62. The mean haemoglobin in Mathapati et al. and Nath and Sheth was 5.6 in each, which was comparable to our study.[1,4] The mean total leukocyte count in the present study was 2,742. The mean total leukocyte counts in Mathapati et al. and Nath and Sheth were 3,434 and 3,535, respectively.[1,4] The mean platelet count in the present study was 51352.1. The mean platelet counts in Mathapati et al. and Nath and Sheth were 39236.8 and 38269.9, respectively.[1,4]

Serum vitamin B_{12} and serum folic acid levels were done in all patients in the present study. The mean serum vitamin B_{12} was 92.87 and mean folic acid level was 3.85 in the present study. The mean serum vitamin B_{12} was 150.5 and the mean folic acid level was 2.72 in study by Mathapati et al. and 150.66 and 2.729, respectively in the study by and Nath and Sheth.[1,4]

Serum vitamin B_{12} and folic acid deficiency was the leading cause of pancytopenia in the present study, which was comparable to other studies. Obaji and Al-Ismail from the University Hospital of Wales, U.K, published a case report on a 26-year-old pregnant woman presenting with severe pancytopenia due to folate deficiency with complete recovery observed after folic acid replacement.[5] Van de Velde et al. from the University Hospital of Antwerp, Belgium, published a case report on gravida 6 para 5 living 5 with 38 week with severe pancytopenia caused by ineffective hematopoiesis because of folate and vitamin B_{12} deficiency.[6] Dragusin et al. from Paris Descartes University, France, published case report of Primigravida with 28 weeks with pancytopenia secondary to folate and vitamin B_{12} deficiency with intrauterine growth restriction ($<5^{th}$ percentile), oligohydramnios, and absent end-diastolic umbilical flow.[7] Teklu et al. from Ababa University, Ethiopia reported case series of 7 pregnant patients with pancytopenia with megaloblastic anemia.[8] All patients showed clinical improvement with RBC, plasma and platelet transfusions, folate and B_{12} treatment.

In the present study, there were 2 cases of pancytopenia associated with COVID-19 infection. Agarwal et al. reported 2 cases of pregnant women with pancytopenia associated with COVID-19 infection and vitamin B_{12} and folic acid deficiency.[9] Issa et al. reported persistent pancytopenia in an immunocompromised patient who had severe COVID-19 infection with cytokine storm.[10] Additionally, an aspirate of bone marrow revealed severe acute respiratory syndrome-coronavirus-2.

CONCLUSION

Although it is uncommon, pancytopenia during pregnancy carries a higher risk of maternal morbidity and unfavorable fetal outcomes. Routine prenatal check-ups should include routine evaluation of the mother's hemoglobin, total leucocyte count, and platelet count in order to facilitate prompt diagnosis and promote a favorable feto-maternal outcome. This study observed that most of the participants were vegetarian by diet with Vit-B_{12} deficiency followed by folate deficiency leading to pancytopenia. Our study showed that vitamin B_{12} and folic acid improved the outcome of patients with pancytopenia. Hence, pregnant women with pancytopenia can be safely treated with vitamin B_{12} and folic acid even when their levels cannot be assessed. Appropriate nutritional guidance and balanced meal plans, even derived from plants can prevent micronutrient deficiencies and adverse outcomes like pancytopenia.

Limitation of the study is that outpatients were not included in the study group and only inpatients were included.

Strength of the study is that the outcome of the study showed most of the participants were vegetarian by diet with Vit-B_{12} deficiency followed by folate deficiency leading to pancytopenia, and vitamin B_{12} and folic acid improved the outcome of patients with pancytopenia. We have included all obstetric patients with pancytopenia attending our hospital, investigated the cause with available resources and come to the most common and treatable cause. This can be applied to the general population of obstetric patients with pancytopenia.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Madhu Jadaiswamy;* ***Design:*** *Madhu Jadaiswamy;* ***Control/Supervision:*** *Madhu Jadaiswamy;* ***Data Collection and/or Processing:*** *Rachitha M Prasad, Madhu Jadaiswamy;* ***Analysis and/or Interpretation:*** *Madhu Jadaiswamy;* ***Literature Review:*** *Rachitha M Prasad;* ***Writing the Article:*** *Rachitha M Prasad, Madhu Jadaiswamy;* ***Critical Review:*** *Madhu Jadaiswamy;* ***References and Fundings:*** *Rachitha M Prasad;* ***Materials:*** *Rachitha M Prasad.*

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