

SOME OBSERVATIONS ON SEVERE ANAEMIAS IN PREGNANCY IN BIHAR

by

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In asking me to deliver the fourteenth Sir Kedarnath Das Memorial Oration you have bestowed upon me a great honour. It has been a matter of privilege for me to learn most of his techniques in operative obstetrics and gynaecological practice. Though not a direct student of Sir Kedarnath, yet I had ample opportunities to know his methods through my respected teachers. Prof. Duncan Murdoch always spoke high of his monograph on obstetric forceps which still stands unparalleled in the world of literature today. In fact Prof. Murdoch was a great exponent of the instrument devised by him in respect of its suitability for the mothers and babies of this part of the country. The late Prof. Akhlnath Sarkar and Prof. U. P. Gupta had the privilege of directly learning from Sir Kedarnath and through them the knowledge disseminated even to the undergraduate students of Prince of Wales' Medical College, Patna. Therefore, I have a claim to be called a student of Sir Kedarnath.

To you I am most grateful for having owned me once again as a member of the old family of the State of Bengal, Bihar and Orissa.

The name of Sir Kedarnath is carried through most of the textbooks of Obste-

trics all over the world for his successful attempts to save the labouring mothers and reward them with live children. His monumental work in reducing the maternal and foetal mortality remains unchallenged upto now. My attempts towards the same goal in Bihar was to a large extent directed in understanding, prevention and treatment of anaemia complicating pregnancy. That is why I selected "Some Observations on Severe Anaemias in Pregnancy in Bihar" as a subject of oration associated with the name Sir Kedarnath Das.

Anaemia manifests itself in different forms in different parts of the globe. When it complicates pregnancy, the polymorphism is even greater. In our sub-continent where so much variation is encountered in food and living habits from one State to another, it is no wonder that the cause of anaemia also varies. In an earlier series of investigations on anaemias complicating pregnancy (Upadhyay, 1944) it was found to be commoner in primigravida when the individual parity was considered. Anaemia was more prevalent in women taking a diet poor in proteins as well as other nutrients. The commonest cause of maternal mortality and premature deliveries was also severe anaemia complicating pregnancy. The pathogenesis of this disease has been elaborately investigated by various workers and these findings have greatly added to our knowledge. In the present discus-

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sion it is proposed to dwell upon some pertinent features of anaemia complicating pregnancy which are significantly borne out by clinical observations (Upadhyay, 1944, 1956, and 1969).

Material and Methods

It is hardly necessary to define the types of cases studied because these were all severely anaemic pregnant women at the last trimester of pregnancy with anaemia and haemoglobin below 5 gm. per 100 ml., without any evidence of pre-eclamptic toxæmia. During the period from 1942 onwards 121 full time normal pregnancy cases were studied for use as a control whenever required and 475 cases of anaemia complicating pregnancy were investigated by various methods which gradually came in the field as a result of advancement in clinical haematology.

From each patient, an accurate history of the usual diet, economic status and living condition was recorded. Stool and urine were examined as a routine. Haemoglobin content was estimated, total red

cell count was done, packed cell volume was measured and from the buffy coat, a smear was prepared for determination of lobe average index and enumeration of hypersegmented neutrophils. On the basis of the above values, the mean corpuscular volume, mean corpuscular haemoglobin and mean corpuscular haemoglobin concentration were calculated. A peripheral smear was studied for the detection of morphological abnormalities of blood cells. Bone-marrow smear was obtained by the puncture of the iliac crest. Total serum protein, albumin and albumin-globulin ratio were determined by biuret method and paper electrophoresis respectively. Estimation of the serum folic acid content was done by microbiological assay with lactobacillus casei. Liver function tests included serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, serum bilirubin estimation, serum alkaline phosphatase determination, standard bromsulphthalein excretion test and thymol turbidity test. Liver biopsy was obtained for histological study by the Vim-Silverman's needle. Gastric analysis was done in 130 cases of severe anaemia complicating pregnancy. No evidence of achlorhydria was noted.

Observations and discussion

Haematological studies and bone-marrow smear examination showed that 80 per cent of the cases were macrocytic anaemia (Table I). Dimorphism was

TABLE I
Distribution of the cases of different types of anaemia complicating pregnancy

| Type of anaemia | No. of cases. | Percentage. |
|--------------------------------|---------------|-------------|
| Macrocytic | 76 | 16.00 |
| Dimorphic | 304 | 64.00 |
| Microcytic hypochromic | 95 | 20.00 |

cell count was done, packed cell volume was measured and from the buffy coat, a smear was prepared for determination of lobe average index and enumeration of hypersegmented neutrophils. On the basis of the above values, the mean corpuscular volume, mean corpuscular haemoglobin and mean corpuscular haemoglobin concentration were calculated. A peripheral smear was studied for the de-

present in 80 per cent of the cases showing macrocytic blood picture. This correlates with the clinical history which showed that the diet in severely anaemic pregnant mothers not only lacked in iron and folic acid, but also in proteins.

Serum protein estimation in 121 normal pregnant women and 475 cases of severe anaemia complicating pregnancy showed that the mean total serum pro-

tein content in severely anaemic pregnant women was 2.7 gm. per 100 ml. lower than in normal pregnancy which on statistical analysis is highly significant ($P < 0.001$) (Table II). Mean albumin content in severe anaemias complicating pregnancy was 1.5 gm. per 100 ml. lower than in normal pregnancy which is also highly significant ($P < 0.001$) (Table III). There was reversal of the albumin-globulin ratio (Table IV). The mean albumin-globulin ratio diminished from 1.05 in normal pregnancy to 0.77 in severe anaemia complicating pregnancy ($P < 0.001$). The diminution of total serum protein was thus found to be mainly due to the reduction of albumin fraction of the serum. The significance of

this hypoproteinaemia and hypoalbuminaemia in the system is very grave. The osmotic pressure of serum diminishes leading to anasarca. It indicates inability of the liver to maintain the normal requirement of serum albumin level. This leads to derangement of such vital body functions as cellular metabolism, growth and haematopoiesis. Hypertrophy of the uterus and breasts, and rapid growth of the foetus during last trimester of pregnancy worsen the whole picture.

It has been observed that an adequate serum protein level is imperative for the proper functioning of the bone-marrow. Correlating the serum protein content with the activity of the bone-marrow it was found that when the serum protein

TABLE II
Mean total serum protein (Gm/100 ml) in normal pregnancy and severe anaemia complicating pregnancy

| Types of cases | Number of cases | Mean (Gm/100 ml) | S D | S E | P-value. |
|--|-----------------|------------------|------|-------|-----------------|
| Normal pregnancy | 121 | 6.2 | 1.41 | 0.12 | Less than 0.001 |
| Severe anaemia complicating pregnancy. | 475 | 3.5 | 1.22 | 0.056 | |

TABLE III
Mean serum albumin content (Gm/100 ml) in normal pregnancy and severe anaemia complicating pregnancy

| Types of cases. | Number of cases | Mean (Gm/100 ml) | SD | SE | P-value. |
|--|-----------------|------------------|------|-------|--------------------------|
| Normal pregnancy | 121 | 3.1 | 0.98 | 0.089 | Less than 0.001 0.001 |
| Severe anaemia complicating pregnancy. | 475 | 1.6 | 0.18 | 0.008 | |

TABLE IV
Mean albumin—globulin ratio in normal pregnancy and severe anaemia complicating pregnancy

| Types of cases | Number of cases | Mean | SD | SE | P-value |
|--|-----------------|------|------|------|-----------------|
| Normal pregnancy | 121 | 1.05 | 0.36 | 0.03 | Less than 0.01. |
| Severe anaemia complicating pregnancy. | 475 | 0.77 | 0.04 | 0.01 | |

level was below 3.5 gm. per 100 ml., the bone-marrow was hypoplastic. In a study of 315 cases it was found that the bone-marrow was hypoplastic in 84 per cent of the 200 cases where the total serum protein content was equal to or below 3.5 gm. per 100 ml. (Table V). The reticulocyte response following treatment was also recorded and it went up only when the serum protein content could be raised over 3.5 gm. per cent. These observations suggest that if the serum protein is below 3.5 gm. per cent, haematopoiesis is almost at a stand still, no matter how much iron, liver extract or folic acid is given to stimulate it.

The diminution of the total serum protein in general and the serum albumin in particular is indicative of associated hepatic dysfunction. Liver function test in 50 cases of severe anaemia complicating

pregnancy (Table VI) showed significant rise of S.G.O.T. in 26 per cent and S.G.P.T. in 54 per cent of cases of severe anaemia complicating pregnancy, compared with normal pregnancy. This suggests that leakage of these enzymes into the serum occurred following damage of hepatic cells in anaemia. The standard bromsulphthalein test showed raised retention of the dye in 50 per cent cases of severe anaemias complicating pregnancy compared with normal pregnancy. Thymol turbidity test was moderately raised in over half the cases. The serum alkaline phosphatase was within normal limits in 88 per cent of cases and serum bilirubin was below 1 mg. per cent in 56 out of 58 cases. However, the liver is an organ with tremendous reserve and only gross cellular damage will lead to severe impairment of liver function. At least

TABLE V
Bone-marrow picture of 200 cases with serum protein of 3.5 gm. percent or less

| Cases with serum protein content of 3.5 gm. per cent or less | Cases with hypoplastic bone-marrow | | Cases with evidence of active bone-marrow | |
|--|------------------------------------|------------|---|------------|
| | Number | Percentage | Number | Percentage |
| 200 | 168 | 84 | 32 | 16 |

TABLE VI
Results of the liver function tests in normal pregnancy and different types of anaemia complicating pregnancy

| Liver function tests | Normal pregnancy. | Different types of anaemia complicating pregnancy |
|------------------------------------|-------------------|---|
| S. G. O. T. (I. U.) | 5 — 20 | 5 — 25 |
| S. G. P. T. (I. U.) | 5 — 15 | 3 — 40 |
| Total serum bilirubin (mg/100 ml.) | 0.3 — 0.8 | 0.2 — 0.95 |
| B. S. P. excretion test | 5% | 3 — 7% |
| Thymol turbidity test (units) | 0 — 4 | 3.2 — 6.5 |
| Alkaline phosphatase (K. A. unit) | 3 — 13 | 2 — 15 |

these liver function tests could be regarded as an indication of the presence of abnormal process in that organ in severe anaemia complicating pregnancy.

In order to correlate the functional derangement of the liver with its structure, liver biopsy was done in 35 cases of severely anaemic pregnant women. None of the cases had any evidence of pre-eclamptic toxæmia. Liver biopsy in severe anaemia is potentially dangerous and may be fatal. Bleeding time, clotting time and prothrombin time were carefully assessed in every case. Strict asepsis was maintained and a bottle of compatible blood was also kept ready.

The liver in 30 out of 35 cases showed histological changes in severe anaemia complicating pregnancy. Liver structure was maintained in all the cases. There was dilatation of central vein in 20 cases (Fig. 1), sinusoidal dilatation in 15 cases (Fig. 2), cloudy swelling in 15 cases (Fig. 3), hydropic changes in cell cytoplasm in 12 cases (Fig. 4), fatty infiltration in 10 cases

(Fig. 5), focal round cell infiltration in 5 cases (Fig. 6) and mild necrosis in 5 cases (Fig. 7). Kupfer's cells were markedly prominent in 7 cases (Fig. 8). The prominence of Kupfer's cells may be an indication of excess phagocytosis in causing release of more iron, probably to meet the demands of the foetus which does not show any evidence of anaemia even when the mother is severely anaemic (Ugadhay, 1945). The overall picture suggested that anoxia, congestion and malnutrition are responsible for these structural and functional derangements in liver in cases of severe anaemias complicating pregnancy.

In course of the current investigations the diagnostic importance of serum folic acid estimation, leucocytic lobe average determination and enumeration of hypersegmented neutrophils in peripheral smear for detection of megaloblastic erythropoiesis were compared. The serum folic acid levels in normal pregnancy and different types of anaemias are shown in Tables VII, VIII and IX. The diminution of serum folic acid levels in megaloblastic

TABLE VII
Range and mean values of total serum folic acid content ($\mu\text{g}/\text{ml}$) in normal pregnancy and different types of anaemia complicating pregnancy

| Types of cases | Number of cases | Range | Mean | SD | SE | P-value of the difference of mean between normal pregnancy and different types of anaemia |
|---|-----------------|------------|------|------|------|---|
| Normal pregnancy | 22 | 2.2 — 13.2 | 6.7 | 3.46 | 0.76 | |
| Megaloblastic anaemia complicating pregnancy. | 12 | 1.0 — 4.2 | 2.5 | 1.14 | 0.32 | Less than 0.001 |
| Dimorphic anaemia complicating pregnancy. | 47 | 1.2 — 9.1 | 3.8 | 2.10 | 0.30 | Less than 0.01 |
| Iron deficiency anaemia complicating pregnancy. | 15 | 1.4 — 10.1 | 0.50 | 2.68 | 0.67 | Not significant. |

TABLE VIII

Range and mean values of the stable factor of the serum folic acid content (mug/ml) in normal pregnancy and different type of anaemia complicating pregnancy

| Types of cases | Number of cases | Range | Mean | SD | SE | P-value of the difference of mean between normal pregnancy of different types of anaemia. |
|---|-----------------|-----------|------|------|------|---|
| Normal pregnancy | 22 | 1.5 — 5.2 | 2.8 | 1.2 | 0.60 | |
| Megaloblastic anaemia complicating pregnancy. | 12 | 1.0 — 3.0 | 1.9 | 0.6 | 0.17 | Not significant. |
| Dimorphic anaemia complicating pregnancy. | 47 | 1.0 — 3.9 | 2.0 | 0.98 | 0.14 | Not significant. |
| Iron deficiency anaemia complicating pregnancy. | 15 | 1.2 — 4.8 | 2.6 | 1.3 | 0.33 | Not significant. |

TABLE IX

Range and mean values of the labile factor of the serum folic acid content (mug/ml) in normal pregnancy and different types of anaemia complicating pregnancy

| Types of cases | Number of cases | Range | Mean | SD | SE | P-value of the difference of the mean between normal pregnancy and different types of anaemia. |
|---|-----------------|-----------|------|------|------|--|
| Normal pregnancy | 22 | 0.6 — 9.9 | 3.9 | 2.96 | 0.63 | |
| Megaloblastic anaemia complicating pregnancy. | 12 | 0.0 — 1.5 | 0.6 | 0.40 | 0.11 | Less than 0.001 |
| Dimorphic anaemia complicating pregnancy. | 47 | 0.0 — 6.2 | 1.7 | 1.20 | 0.17 | Less than 0.01 |
| Iron deficiency anaemia complicating pregnancy. | 15 | 0.2 — 5.3 | 2.9 | 1.66 | 0.42 | Not significant. |

blastic anaemia and dimorphic anaemia complicating pregnancy is mainly due to the reduction of the labile factor of folic acid (Table IX). The stable factor does not show any significant variation (Table VIII). Considering 4 mug/ml. of total serum folic acid as a critical level the

wide spread of values in individual cases of normal pregnancy, megaloblastic anaemia, dimorphic anaemia and iron deficiency anaemias complicating pregnancy show that a diagnostic significance about the type of anaemia could not be attributed to serum folic acid estimation.

Determination of leucocytic lobe average and enumeration of hypersegmented neutrophils in peripheral smear were also employed in order to assess their place in the diagnosis of the type of anaemia. Lobe average index of more than 3 was observed in 100 per cent cases of megaloblastic anaemia, 70 per cent cases of dimorphic anaemia and 30 per cent cases of iron deficiency anaemia complicating pregnancy. Therefore, an increase of lobe average index, although found in majority of the cases of megaloblastic and dimorphic anaemia, was also found to be so in one-third of the cases of iron deficiency anaemia.

Considering the enumeration of hypersegmented neutrophils in peripheral smear, it was found in 100 per cent cases of megaloblastic anaemia, 70 per cent cases of dimorphic anaemia and in only 6 per cent cases of iron deficiency anaemia. Obviously enumeration of hypersegmented neutrophils in peripheral smear is a more accurate guide for the diagnosis of macrocytic anaemia of pregnancy, including those having megaloblastic bone-marrow reaction. It is easier to count the number of hypersegmented cells in peripheral smear accurately than the number of lobes in leucocytes, because quite often the lobes overlap. The fallacy due to a shift to the left of the leucocytic lobe average value in normal pregnancy cases can be easily overcome by counting the number of hypersegmented cells. The lobe average index of individual cases varies from one laboratory to another, which is not so with hypersegmented neutrophils. Indeed, it may have to be remembered that hypersegmentation of neutrophils may be rarely found as a congenital disorder or in cases of renal disease.

Bone-marrow smear examination findings were also compared with serum folic

acid levels, leucocytic lobe average index and enumeration of hypersegmented neutrophils in peripheral smear. With megaloblastic bone-marrow, the serum folic acid was less than 4 $\mu\text{g/ml}$. in 70 per cent cases, but in cases with serum folic acid level of 4 $\mu\text{g/ml}$. or less, the marrow was normoblastic in 40 per cent cases. Correlating the leucocytic lobe average index of more than 3, the bone-marrow was megaloblastic in 67.7 per cent cases. But taking the number of hypersegmented neutrophils of more than 3 per cent, the bone-marrow was megaloblastic in 86.37 per cent. Therefore, correlating with the bone-marrow smear examination findings, the presence of more than 3 per cent hypersegmented neutrophils in peripheral smear is the most accurate indication of megaloblastic bone-marrow reaction. If the peripheral smear shows more than 3 per cent hypersegmented neutrophils, a bone-marrow smear examination should be performed to detect the type of abnormal activity in the bone-marrow.

In the light of the present observations it may be stated that in the majority of cases of severe anaemia complicating pregnancy, the deficiency of protein occurs *pari passu* with those of iron and/or folic acid. The bone-marrow becomes hypoplastic with the evidence of dimorphic anaemia. The prognosis of severe anaemia complicating pregnancy is grave with very bleak chances of survival when congestive cardiac failure supervenes. Premature labour is frequent and the immediate puerperal period is the most critical time. Therefore, these cases call for accurate diagnosis and vigorous treatment, no matter what may be the period of gestation. The importance of routine administration of iron to expectant mothers had been accepted as an important step in the prophylaxis against anaemia complicating pregnancy. The

role of folic acid and protein should also be kept in mind. Clinical experience shows that the anaemic pregnant women are somewhat more prone to develop severe pre-eclamptic toxæmia. It may be the manifestation of anoxia in chorio-decidual space, which lights up another chain of events culminating in pre-eclamptic toxæmia. The liver being the main detoxicating organ of the body, whatever noxious agent predisposes pregnant women to pre-eclamptic toxæmia, is not

detoxicated by the liver which is already damaged as a result of anaemia complicating pregnancy.

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See Figs. on Art Paper I-II