MEGALOBLASTIC ANAEMIAS IN PREGNANCY

(In Delhi)

by

ANUSUYA DASS,* M.B.B.S., F.R.C.O.G.

INDIRA BHATT,** M.S.C.M.S. (Wise)

and

BALBIR DHALIWAL,** M.B.B.S., D.G.O., M.D.

The problem of anaemias in pregnancy has been of perpetual interest since the last forty years all over the world. Among the various types of anaemia during pregnancy dyshaemopoietic anaemias are the commonest. The deficiency may be of various factors like iron, folic acid, vitamin B_{12}, vitamin C and proteins.

Since the recognition of dimorphic anaemias, high incidence of this variety of anaemia is being reported every year in India. Das Gupta and Chatterjee from Calcutta (1953), and Menon from Madras (1954) reported an incidence of 58.5% and 66.3% respectively. Raj in the same year (from Nagpur) reported a figure of 52%, while Menon (1965) found that 60.0% of his cases belonged to this group. Due to the ever increasing awareness of this type of anaemia, it was considered worthwhile to study megaloblastic anaemias in Delhi.

Material and Methods

In all, 143 cases of anaemia of pregnancy, who were admitted in the antenatal wards, were studied. A detailed present and past obstetric and family history was taken. The present history included details about the time of onset of breathlessness, anorexia, fatigue, oedema feet, vomiting and diarrhoea. A detailed menstrual and obstetric history was recorded regarding increased menstrual bleeding or excessive blood loss at previous abortions or labour. A past history of bleeding gums, epistaxis, malaria, recurrent episodes of anaemia in previous pregnancies and the use of tonics or exposure to drugs and chemicals were enquired into.

A dietetic history was taken in all the cases with special reference to the intake of first class protein. A thorough clinical examination was done in every case and the following haematological and biochemical investigations were carried out:

Haemoglobin, red blood cells, white blood cells, platelet count, P.C.V., M.C.H.C., reticulocyte count, peri-

*Prof. & Head of the Department of Obstetrics & Gynaecology.

**Reader in Biochemistry.

Maulana Azad Medical College, New Delhi.

Paper read at the 13th All-India Obstetric & Gynaecology Congress held at Patna in January 1966.

pheral smears, serum bilirubin (whenever the serum had an icteric tinge), osmotic fragility of red blood cells, bone marrow biopsy and serum iron (determined by a modified method of Barkan (1940) involving the use of O-phenanthroline), serum iron-binding capacity and the percentage saturation of transferrin were estimated whereever possible.

Observations and Discussion

Out of 143 cases studied, 76 (53.2%) were suffering from pure iron deficiency, 57 (39.8%) dimorphic, 7 (4.9%) macrocytic and 3 (2.1%) were refractory anaemia. For practical purposes the dimorphic and the macrocytic anaemias were considered together. This would mean that no less than 64 out of 143 cases were of the megaloblastic type giving an incidence of 44.5%. Reporters on megaloblastic anaemias of pregnancy have also included the dimorphic variety in their series of cases. A comparison with the Indian workers is given in Table 1.

TABLE I

Incidence of Megaloblastic Anaemias

Author	Place	Year	Incidence
Choudhuri & Manglik	Agra	1938	65.8% of anaemia cases
Napier & Mazumdar	Calcutta	1938	40.2%
Napier & Neil Edwards	,,	1941	14.6%
Das Gupta & Chatterjee	,,	1953	58.5%
Menon & Chandrashekran	Madras	1954	66.3%
Chatterjee	—	1960	39.2%
Menon et al	Madras	1965	60.0%
Mehrotra et al	—	1965	54.0%
Present series	Delhi	1965	44.5%

It can be seen that the lowest incidence is reported from Calcutta and maximum from Madras, while the incidence in Delhi is also relatively low. These differences may be due to variations in climate and food habits. Menon (1965) determined serum B_{12} and folic acid levels in cases of anaemia. He found a statistically significant fall in serum folic acid but not B_{12} levels indicating that folic acid deficiency was the major causative factor even in normal pregnancy. He detected a reduction in serum folic acid and stressed the necessity of routine administration of folic acid along with iron during pregnancy. Chatterjee (1958) however, demonstrated that 50% of his cases had vitamin B_{12} deficiency.

Regarding the effect of age on the incidence of anaemia, it was found that it was lowest in the age group 15-19 years (7.8%) and maximum at 20-29 years (56.3%), the period of maximum fertility. After 30 years the incidence fell to 35.9%. Most of the workers, Napier and Edwards (1941), Giles and Burton (1960), Rajasuriya *et al* (1960) also give the mean age between 20-29 years. Das Gupta and Chatterjee (1953) and Raj (1954) found no correlation with age.

Parity does not appear to play any part. Maximum number of cases, 34

(53.2%), was found in the 2nd to 5th parae, while an equal number 15 (23.4%), were found in the primi-

grades of anaemia. This view has been supported by Giles and Burton (1960) and Ainley (1961).

TABLE II

Showing the Average Value in High Serum Iron Group

No. of patients	Maximum	Minimum	Mean ± S.D.	S.E.
Hb %	8.5	3.0	6.44± 1.7	0.06
PCV %	36.0	11.0	24.9 ± 7.6	0.3
MCHC %	35.0	21.0	24.9 ± 3.1	0.1
Serum iron m.c.g.	760.0	120.0	312.8 ± 160.4	6.4
U.I.B.C. m.c.g.	480.0	0.0	230.4 ± 180.4	7.2
T.I.B.C. m.c.g.	760.0	312.0	543.5 ± 127.8	5.1
Percentage saturation of Transferrin	100.0	20.7	55.5 ± 27.07	1.08

parae and in multiparae after the 6th pregnancy. Choudhury (1938), Upadhyay (1944) and Giles and Shuttleworth (1958) found the greatest number of cases in primiparae. Das Gupta and Chatterjee (1953) found the highest incidence in 2nd parae while Kothari and Bhende (1952) and P. Raj (1954) failed to find any correlation with parity.

The main presenting symptoms were oedema, dyspnoea or oedema associated with dyspnoea. Severe oedema was seen in 88% of the cases. There was no particular correlation between the degree of oedema, dyspnoea and the serum iron levels.

Haematological findings

Eleven out of 64 cases had haemoglobin levels below 3.90 gm% and 21 (32.8%) had the level between 4-5.9 gm%, 24 (37.5%) between 6-7.9 gm% and 8 (12.5%) between 8.8-9 gm%. Table II indicates that megaloblastic anaemias can occur with higher levels of haemoglobin and must therefore be suspected in all

The peripheral picture in all but 5 cases was macrocytic hypochromic, typically representing the dual deficiency. In 5 cases the peripheral smears were misleading. The two deficiencies distorted the blood picture in two different directions neutralising the effect of each other. Thus the presence of these deficiencies was not reflected clearly in the changes in the smear. The initial smears in 4 cases denoted a normocytic morphology and so were primarily included as iron deficiency anaemias. Ten days of treatment with iron produced a minimal response and the bone marrow at this juncture revealed the megaloblastic nature of the anaemia. These findings emphasize the value of marrow puncture in cases of anaemia, especially those refractory to iron therapy. These findings have also been confirmed by other workers, Das Gupta *et al* 1953, Raj 1954 and Menon 1954. The bone marrow in 7 (4.9%) (of all cases) was frankly megaloblastic, whereas in the rest it

presented a dimorphic picture.

Macrocytic anaemia in our study has been diagnosed on the basis of morphology seen in the peripheral blood and bone marrow. Herbert (1963) emphasized that the macrocytic changes in the peripheral blood smear and macrocytosis occur much earlier than the changes in bone marrow morphology, which is not in agreement with our findings and that of other workers. Callendar (1944) and Ainley (1961) advocated the identification of megaloblasts in the peripheral smear as a substitute for bone marrow examination. The above has already been stressed by Choudhury (1938). The diagnostic significance of hypersegmented neutrophils has been reported by Napier and Edwards (1941), Callender (1944) and P. Raj (1954). Das Gupta (1954) and Mckenzie and Abbot employed it as a screening procedure.

An interesting feature in this series was the variation in the serum iron levels in 33 cases of dimorphic anaemia.

In 75% of the cases the serum iron level was above 120 mcg% while in 25% the value was below 120 mcg% and even as low as 12 mcg%. Giles and Burton (1960) noted high serum iron levels with bone marrow showing a normoblastic reaction, necessitating the use of folic acid and proving the dimorphic nature of the anaemia. Das Gupta *et al* (1954) noted that serum iron in macrocytic anaemia ranged from 104.1 mcg% to 134.6 mcg% while Callendar (1944) gave a figure of 95-270 mcg%. The low levels are due to the deficiency of iron as well. Wilmott and Ramaswamy (1965) noted that the average serum iron in dimorphic anaemia was higher than in the iron deficiency group. This is in agreement with our findings. Chatterjee *et al* (1953) Das Gupta (1954), P. Raj (1954) and Menon (1954 and 1965) found normoblastic marrow with macrocytic hypochromic anaemia but do not mention the variations in the serum iron content in these patients. Thus it is worth while to perform serum iron estimations even if the marrow is normoblastic. This would detect folic acid deficiency earlier. In places where there are no facilities for bone marrow and serum iron studies, it must be mentioned that iron therapy aids in diagnosing megaloblastic anaemias, just as folic acid helps to unmask the latent iron deficiency. The level of the serum iron would depend on whether the predominant deficiency was that of folic acid and/or B_{12} or of iron. Moreover it was found that in cases exhibiting high serum iron levels, the bone marrow contained more of megaloblastic cells as compared to those where the serum iron levels were comparatively low and in these there was predominance of basophlic normoblasts. This again goes to show that in the former group, folic acid deficiency is dominant whereas in the latter lack of iron is the major factor Table II.

Errors in serum iron estimations were excluded by running a standard series throughout. Increased fragility of the red cells was excluded by doing the quantitative fragility test, which was within normal limits. In 5 of these cases (exhibiting very high serum iron levels), we decided to administer only folic acid orally, 20

mgm. per day, along with daily injections of liver extract 2 c.c. intramuscularly. The response was assessed by weekly serum iron estimations. The serum iron fell rapidly, and concomitantly there was a rise in the haemoglobin and haematocrit levels.

In some cases the serum iron levels fell even below 70 mcg%, the lower limit of the normal, Table III. When this occurred supplementary iron therapy was started and improvement in haemoglobin and haematocrit continued. Such a response has been reported by Hawkins (1955) in pernicious anaemia. This fall in serum iron is probably the earliest sign of a haematological response, following a specific therapy, for bone marrow reversion is not complete till 32-72 hours (Davidson *et al* 1942) and the reticulocyte response does not occur for several days. Perhaps the explanation for the fall of serum iron to a low level is that the rate of release of iron from the stores, possibly by enzymatic action, cannot keep pace with the increased demand. This test is an index of the increased turnover of iron in the body and a low serum iron is thus a measure of erythropoietic activity. This rapid fall that follows specific therapy in anaemia due to folic acid or B_{12} deficiency, is a sensitive indication of early marrow response (Hawkins 1955). All cases of dimorphic and macrocytic anaemia responded well to folic acid and iron therapy showing that folic acid deficiency is the cause of megaloblastic anaemia.

Recently Parikh (1958), Chatterjee (1960) and Menon (1965) have shown by Vitamin B_{12} and folic acid estimations that there is no significant reduction of serum B_{12} levels in these patients and the deficiency is mainly of folic acid. We, too are in agreement with the above authors, though we could not substantiate our results with estimation of serum folic acid and B_{12} levels as would have been the ideal.

TABLE III

Average Values for the Low Serum Iron Group

No. of patients	Maximum	Minimum	Mean ± S.D.	S.E.
Hb %	8.8	3.25	6.0 ± 2.09	0.2
PCV %	30.0	10.0	23.25± 8.03	1.003
MCHC %	42.5	19.0	26.4 ± 7.09	0.8
Serum iron m.c.g.	112.0	12.0	58.7 ± 31.3	3.9
U.I.B.C. m.c.g.	520.0	240.0	415.0 ± 95.4	11.9
T.I.B.C. m.c.g.	570.0	300.0	473.7 ± 85.6	10.7
Percentage saturation of Transferrin	25.9	2.4	13.06± 7.7	0.96

Summary and Conclusions

1. A total of 143 anaemic pregnant patients were studied in detail. Out of these, 76 (53.2%) belonged to pure iron deficiency anaemia, 57 (39.8%) were dimorphic anaemia, 7 (4.9%) macrocytic anaemia and 3 (2.1%) were refractory anaemia.

2. Maximum number of cases, 36 out of 64 i.e. 56.3%, were in the age

group of 20.29 years. No correlation could be found between the type of anaemia and parity.

3. Symptoms specific for dimorphic anaemia were dyspnoea, oedema or a combination of both.

4. The serum iron values in cases of dimorphic anaemia showed characteristic readings. In 75.8% of the cases, the serum iron levels were high, whereas in 24.2% they were low. These two types of values were due to the relatively increased deficiency of folic acid or iron.

5. All cases responded well to folic acid and iron therapy. In 5 cases with high serum iron levels there was a significant drop with an increase in the haemoglobin and haematocrit with folic acid therapy, proving that high levels of serum iron in the cases were not due to any faulty technique or intravascular haemolysis, but due to the block in the utilization of iron present in the serum because of absence of folic acid.

6. Certain cases of dimorphic anaemias present difficulties in diagnosis due to the bone marrow morphology not being consistent with the peripheral smear.

In such cases serum iron estimations may be of diagnostic value in unmasking the actual deficiency.

7. Repeated observations of serum iron, especially in cases where it is raised, can be used as a diagnostic procedure by giving folic acid or Vitamin B_{12} therapy. This could be done especially where facilities are not available for estimating the folic acid or Vitamin B_{12} levels in the serum.

Acknowledgments

We wish to thank Professor S. N. Chaudhury, M.B.B.S., D.Phil., Professor of Biochemistry, for providing us with all the laboratory facilities and for his constant advice and guidance on the biochemical aspect of the problem.

We also wish to thank Dr. P. C. Dhanda, Principal, Maulana Azad Medical College, New Delhi, for allowing us to publish this paper.

References

1. Ainley, N. J.: J. Obst. & Gynec. Brit. Comm. **68**: 254, 1961.
2. Callendar, S. T. E.: Q.J.M. **13**: 75, 1944.
3. Chatterjee, J. B.: J.I.M.A. **31**: 4, 1958.
4. Chatterjee, J. B.: Bull. Cal. S.T.M. **8**: 7, 1960.
5. Chatterjee, J. B. and Das Gupta, C. R.: Ind. Med. Gaz. **88**: 127, 1953.
6. Das Gupta, C. R.: Ind. J. Med. Res. **42**: 411, 1954.
7. Das Gupta, C. R. and Chatterjee, (1949) quoted by Das Gupta, et al: Brit. Med. J. **2**: 645, 1953.
8. Davidson, et al: Q.J.M. **11**: 19, 1942.
9. Davidson, et al: Brit. Med. J. **2**: 31, 1942.
10. Giles, M. D., Burton, H. and Mckenzie, A.: Brit. Med. J. **2**: 636, 1960.
11. Giles, C. and Shuttleworth, E. M.: Lancet. **2**: 1941, 1958.
12. Hawkins, C. F.: Brit. Med. J. **1**: 383, 1955.
13. Herbert, V.: New Eng. J. Med. **268**: 201, 368, 1963.
14. Kothari, B. V. and Bhende, Y. M.: Ind. J. Med. Res. **40**: 387, 1953.

15. Mckenzie, A. and Abbot, J.: Brit. Med. J. **2**: 1114, 1960.
16. Mehrotra, T. N., Octavia, G. S. and Wahi, P. N.: J.I.M.A. **45**: 68, 1965.
17. Menon, M. K. K., Chandrashekharan, K.: J. Obst. & Gynec. India. **5**: 17, 1954.
18. Menon, M. K. K.: J. Obst. & Gynec. India. **15**: 127, 1965.
19. Napier, L. E. and Majumdar, D. N.: Ind. J. Med. Res. **26**: 541, 1938.
20. Napier, L. E. and Edward, N. M. I.: Ind. Med. Res. Memoirs. **33**: 1, 1941.
21. Padma Raj: J. Obst. & Gynec. India. **4**: 286, 1954.
22. Padma Raj: J. Obst. & Gynec. India. **5**: 33, 141, 1954.
23. Rajasuriya, K., Nagrathnam, N., Somasundram, M. and Fernando, C. F.: J. Tr. Med. & Hy. **63**: 275, 1960.
24. Upadhyay, S. N.: Ind. Med. Gazi. **79**: 193, 1944.
25. Willmott, M. and Ramaswamy, M.: J. Obst. & Gynec. India. **15**: 36, 1965.