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MEGALOBLASTIC ERYTHROPOIESIS IN PREGNANCY

BY

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During recent years a great deal of attention has been paid to the problem of anaemia in pregnancy. In the antenatal clinic of Sunderland Maternity Hospital, which caters for about 1,800 cases a year, 25% of mothers have at the 32nd week of pregnancy haemoglobin levels below 70%, which Whitby and Britton (1957) regard as the lower limit of normality. Undoubtedly most cases of anaemia in late pregnancy are due to iron deficiency, but there is a growing volume of opinion that many cases are anaemias of megaloblastic type.

As recently as 1951 Thompson and Ungley described 45 cases of megaloblastic anaemia of pregnancy collected over a period of 17 years, while Clark (1952) reported 18 cases in a 7½-year period, an incidence of one case in 1,708 hospital deliveries. During the last five years Lowenstein *et al.* (1955), Scott (1957), Cowan (1957), Forshaw *et al.* (1957), and Forshaw (1958) have reported a much higher incidence of this condition. Giles and Shuttleworth (1958) found one case in 39.5 hospital deliveries, and consider this to be an underestimate of the real incidence.

This increase in the described frequency of megaloblastic anaemia of pregnancy is probably due to increased haematological supervision of expectant mothers at antenatal clinics. Formerly a clinical state of severe illness in pregnancy was described, whereas more recent studies are based on haemoglobin levels, irrespective of symptoms and clinical condition of the patients.

Chanarin *et al.* (1959) produce convincing evidence that megaloblastic anaemia of pregnancy is due to a deficiency brought about by poor absorption of folic acid by the mother or by insufficient dietary supply to meet the needs of mother and foetus. In any deficiency disease, for every case of severe deficiency there must be many cases in which the lack is moderate or even very slight. Goodall (1957) describes cases of moderate anaemia of pregnancy without megaloblastic erythropoiesis but which respond only to folic acid. On the other hand, we have found cases with megaloblastic marrows without anaemia, and because of this we have attempted to assess the frequency of this condition by regular haematological studies on all patients attending antenatal clinics at Sunderland Maternity Hospital over the period of 12 months from September, 1958, to September, 1959.

Method

To reduce the incidence of iron deficiency all patients were given routine oral iron (usually "fergon" tablets, one thrice daily) at first attendance at the antenatal clinic when a haemoglobin estimation was performed. At about the 30th week of pregnancy a further haemoglobin estimation was done, and patients with a level of 70% (10 g./100 ml.) or less had P.C.V. and M.C.H.C. estimations and a stained blood film was examined. Patients showing iron deficiency were given 1 g. intramuscular iron ("imferon") in four divided doses and were re-examined in four weeks (haemoglobin, P.C.V., M.C.H.C., and blood film). On admission to hospital at term or for other obstetrical reasons a haemoglobin and blood film from all mothers was examined.

At any stage particular attention was paid to the following features in the blood films.

1. A normochromic normocytic film with haemoglobin below 70% even after intramuscular iron therapy.
2. Hypersegmented neutrophils.
3. Howell-Jolly bodies.
4. Large erythrocytes (macrocytes), even though they be few.
5. Numerous very large fully haemoglobinized erythrocytes, usually about 12 μ in diameter, were sometimes found after intramuscular iron therapy. This "exaggerated response" to iron is strikingly different from the normal response to iron. It is almost certainly the same feature described by Scott (1954) after intravenous iron therapy in some cases of antenatal anaemia.

If one or more of these features were seen in any blood film a marrow biopsy was carried out.

At least four marrow smears were stained by the May–Grünwald–Giemsa method or by Leishman's stain. Marrow fragments aspirated were sectioned, using the method of Cappell *et al.* (1947), and stained with haemalum and eosin and for iron (Hutchison, 1953).

Results

Marrow Findings.—During the 12 months there were 1,996 hospital deliveries, and 95 marrow biopsies were performed for one or more of the reasons mentioned. 73 cases showing megaloblastic erythropoiesis (40 frankly so, and 33 showing transitional or intermediate change). Two further cases without marrow biopsies are included in the series; both had severe anaemia with megaloblasts in the peripheral blood. The incidence of megaloblastic erythropoiesis is therefore 1 case in 26.6 deliveries. Of the 73 megaloblastic marrows, 56 were associated with a marked cellular hyperplasia and virtually complete absence of fat spaces; the remaining 17 showed a normal histological picture. Iron could be demonstrated in 16 cases only (10 frankly megaloblastic and 6 transitional); the amount was always very small.

Degree of Anaemia.—73% of cases with megaloblastic erythropoiesis had a haemoglobin level in the 50–70% range at the time the marrow biopsy was made (Fig. 1).

Age Incidence.—It is considered that the higher age groups tend to develop megaloblastic anaemia more readily than younger subjects. This series tends to confirm this point of view (Fig. 2): 43 cases (57%) were between 18 and 28 years of age, and 32 cases (43%) were 29 years or more. In common with many maternity departments, most admissions are primiparae, and hence tend to be younger: only 30% of admissions to Sunderland Maternity Hospital are 29 years or more.

Parity and Twin Pregnancies.—The parity of 71 mothers was known: 17 were primiparae, 12 were in the second pregnancy, and 16 in the third pregnancy, while the remaining 26 were pregnant for the fourth time or more. 12 cases of megaloblastic erythropoiesis occurred in mothers who had twin pregnancies: during the period of review there were 50 twin births, an incidence of 24% showing megaloblastic erythropoiesis.

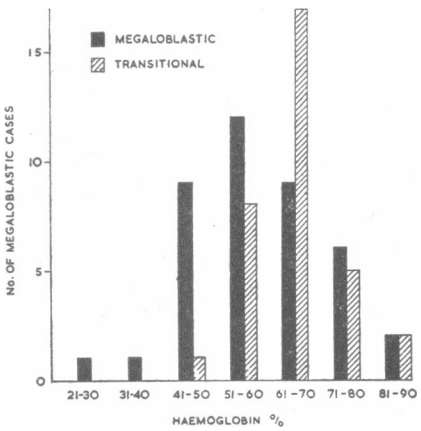

FIG. 1.—Degree of anaemia at time of diagnosis.

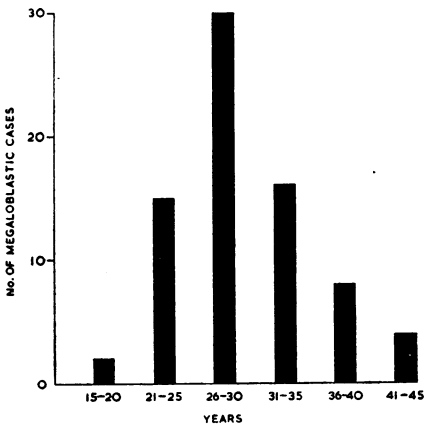

FIG. 2.—Age of incidence.

Time of Diagnosis.—60% of all cases were diagnosed within the period of 10 days before to 10 days after delivery (Fig. 3).

Blood Groups.—The ABO blood group of 67 cases was known (Table I). From this series there does not appear to be any significant association between the liability to develop megaloblastic erythropoiesis and the ABO blood group system. In Addisonian pernicious anaemia there is a significant increase in the incidence of blood group A.

TABLE I.—*ABO Blood Group Distribution of 67 Cases with Megaloblastic Erythropoiesis*

Group A	25 (37·3%)	Group O	30 (44·8%)
,, B	7 (10·4%)	,, AB	5 (7·5%)

TABLE II.—*Number of Cases with Megaloblastic Erythropoiesis During Each Month of Investigation. Total Deliveries are Given in Parentheses*

September	5 (187)	March	8 (168)
October	5 (184)	April	5 (158)
November	4 (136)	May	7 (160)
December	4 (161)	June	9 (168)
January	10 (171)	July	7 (170)
February	4 (151)	August	7 (182)

Seasonal Incidence.—The month in which diagnosis was made did not seem to be significant (Table II).

Complications.—In 68 cases where details were known, 4 (6%) had antepartum haemorrhage, while 29 (42.5%) showed some degree of pre-eclamptic toxaemia. The overall incidence in the unit for antepartum haemorrhage is 2.7% and for pre-eclamptic toxaemia 12.7%. The average haemoglobin level of the 29 cases showing toxaemia was 60%, while the average of 35 cases not showing toxaemia was 61%.

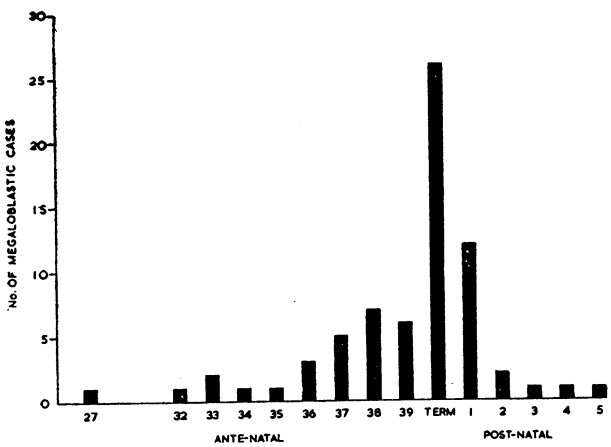

FIG. 3.—Time of diagnosis.

Discussion

This investigation is concerned with the incidence of megaloblastic erythropoiesis in a maternity unit and not with megaloblastic anaemia *per se*. Marrow biopsies were performed on many patients who would not normally be regarded as anaemic; in four cases the haemoglobin was between 80% and 90%. The decision on whether a biopsy was desirable was largely dependent on the appearances of the peripheral blood, and our experience has been that macrocytes in the peripheral blood indicate the possibility of megaloblastic erythropoiesis whatever the haemoglobin level. Megaloblastic anaemia can occur without obvious macrocytosis in the peripheral blood, and because of this our estimate of the incidence of megaloblastic erythropoiesis may be too low; but if patients with a haemoglobin of 65% or less had been selected, as in the series of Giles and Shuttleworth (1958), the incidence would have been 1 case in 38.5 deliveries, a close approximation to the 1 case in 39.6 deliveries which they reported.

In general, interpretation of marrow smears presents little difficulty, but in a few cases prolonged study is necessary. While the differentiation between megaloblastic and transitional erythropoiesis may be convenient for classification, it is nevertheless artificial and seems to be largely a question of degree. Similarly, macronormoblastic erythropoiesis shades into transitional type, and the actual classification eventually depends on individual opinion. In the difficult case the quality of the staining is of the utmost importance, and three or four different smears should be studied. Giant metamyelocytes or giant stab cells and nucleated erythrocytes containing Howell–Jolly bodies (Hutchison

and Ferguson-Smith, 1959) are easily recognized, and are usually indications that megaloblastic changes are present.

The significance of the transitional (intermediate) megaloblast has been the subject of controversy: Dacie and White (1949) and Mollin (1959) believe that transitional megaloblasts are the characteristic marrow reaction where minor deficiencies of vitamin B_{12} or folic acid are present. Fudenberg and Estren (1958) argue that these cells occur because of a superadded deficiency of iron where a deficiency of folic acid or vitamin B_{12} already exists. With both these points of view Kondi and Foy (1959) disagree, as they describe cases of severe anaemia in which only transitional cells can be found, and state that transitional changes are no more frequent in India, where iron deficiency is very common, than in Africa, where iron deficiency is less common. In our experience patients with severe anaemia usually show unequivocal megaloblasts, but this is not always so; conversely, frankly megaloblastic erythropoiesis is sometimes found when the degree of anaemia is slight. Furthermore, we have found transitional-type erythropoiesis where there is a sufficiency of iron and also where a deficiency exists. The "exaggerated macrocytic response" to parenteral iron described by Scott (1954) suggests that when a deficiency of iron in addition to a deficiency of folic acid exists, a macrocytic blood picture appears only when the iron deficiency is being corrected.

Megaloblastic erythropoiesis in pregnancy is probably due to deficiency of folic acid, and there is a growing volume of opinion that folic acid should be given routinely to all cases of anaemia of pregnancy (Lowenstein *et al.*, 1955; Francis and Scott, 1959; Baines, 1959), though opinions vary regarding what haemoglobin level constitutes anaemia. As many of the cases in this series showed only slight anaemia and were detected only just before or just after delivery, the anaemia might have undergone spontaneous remission. This is not always so, as cases of severe megaloblastic anaemia are sometimes not detected until the puerperium.

In this series there have been many cases which showed obstetrical complications other than anaemia; it may be that these complications are aggravated by folic-acid deficiency.

Badenoch *et al.* (1955) suggest that toxaemia may cause anaemia by reducing the ability of the mother's intestine to absorb haemopoietic factors. Another view is that anaemia may be a factor in the development of toxaemia. It might therefore be expected that mothers who develop pre-eclamptic toxaemia would be more anaemic than those who do not. In this series there has been no difference in the average haemoglobin level of the two groups, yet the association between megaloblastic erythropoiesis and toxaemia is high and seems to merit further study.

Summary

In an attempt to find the incidence of megaloblastic erythropoiesis in a maternity unit routine study of blood smears was carried out on antenatal patients showing anaemia and on all patients admitted to the maternity hospital. Marrow biopsies were carried out on all patients showing abnormality of the blood films other than cases of hypochromic anaemia. The incidence of megaloblastic erythropoiesis was found to be 1 case in 26.6 deliveries and 1 case in 4.2 twin deliveries. The condition exists frequently without significant anaemia.

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MULTIPLE-PUNCTURE VACCINATION IN THE NEWBORN WITH FREEZE-DRIED B.C.G. VACCINE

BY

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B.C.G. vaccination has been available in Great Britain for 10 years, and its use in certain groups in the community is now generally accepted. During this period 17,500 newborn infants have been vaccinated with B.C.G. in the University Department of Child Health at St. Mary's Hospital, Manchester. At the outset fresh Danish vaccine was used almost entirely, except for a small amount of freeze-dried vaccine prepared at the Pasteur Institute in Paris, which was kept in readiness as a standby in case the fresh supply should at any time fail. In 1955 a British freeze-dried vaccine was introduced into our immunization scheme, and has now replaced liquid vaccines. In doses of 100.000 to 400,000 viable organisms, given intradermally, it has been found to be effective and free from complications.

Intradermal vaccination will always require a high degree of technical skill, and, if too large a dose is given, or the injection made too deeply, glandular complications or local cold-abscess formation are likely. As the call for B.C.G. vaccination is increased in the underdeveloped countries, a reliable method of inoculation requiring less medical skill would obviously offer great advantages. With this in mind, an investigation of multiple-puncture vaccination of newborn infants was undertaken; for this a more concentrated freeze-dried B C.G. vaccine was used. Since March, 1958, 2,221 babies have been inoculated by this method, which is now increasingly effective and has been free from any complications.

The object of this investigation was to assess those factors which affect the allergy produced by the vaccine, and to attempt to adjust them so that the multiple-puncture technique could be as effective as the intradermal.