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Megaloblastic Anaemia of Pregnancy and the Puerperium

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Introduction

Gestational megaloblastic anaemia is generally thought to be rare. Thus you may be interested to hear something of its occurrence in Dundee where it is found in nearly 2% of women delivered at the Royal Infirmary, the main teaching hospital.

Little is known of the geographical distribution of this gestational type of megaloblastic anaemia, and, indeed, it is only recently that the incidence of Addisonian megaloblastic anaemia has been charted. This survey was made by the College of General Practitioners. For permission to show their map at this conference I am indebted to the Editor of the Journal of that College, and to Dr. E. Scott, Ashford, Kent, who was the originator and author of the work (*Scott*, 1960). The map shows clearly that Addisonian pernicious anaemia is much more frequent in the North of Great Britain than in the South.

Investigation

Let us now turn to the gestational type, and specifically to Dundee.

Materials and Methods

In order to assess the incidence of megaloblastic anaemia of pregnancy, microscopical examination has been made of smears of the buffy coat from the haematocrit of almost all women with a venous haemoglobin level of less than 11 g. per 100 ml. at the antenatal clinic or in the maternity wards at Dundee Royal Infirmary. Severe cases of pre-eclampsia whether anaemic or not were similarly examined. From September 1954 to March 1956

this method was controlled by marrow biopsy, but since then the marrow has been examined only when the buffy coat films were equivocal, or when they were negative in cases in which there was a strong clinical suspicion of megaloblastic anaemia. The technique of examining the buffy coat was as described by *Goodall* (1957), except when examination of erythrophages was required (see discussion), when the method of *Zinkham and Diamond* (1952) was used. The work was carried out with the co-operation of Professor Margaret Fairlie and, later, Professor James Walker and their staffs.

Results

The incidence of megaloblastic anaemia of pregnancy at Dundee Royal Infirmary in six years from June 21st 1954 to June 20th 1960 was 163 cases in 8,877 deliveries, a crude incidence of 1.8%. When certain borderline cases and cases sent from other clinics are removed there is still a corrected incidence of 1.6%. This is probably a little higher than for the whole city, but overall is undoubtedly well over 1%.

Discussion

How does this incidence compare with other areas in the British Isles? The only place with a higher incidence is Stoke-on-Trent: 2.6% (*Giles and Shuttleworth*, 1958). An incidence of 0.5% has been found in Liverpool (*Forshaw, Jones, Chisholm and McGinley*, 1957) and in the Dumfries area of Southern Scotland (*Cowan*, 1957). A rate of 0.3% is recorded in Dublin (*Lillie, Gatensby and Moore*, 1954); Limerick (*Furnell*, 1957); and London (*Discomb*, 1956). The figures for Edinburgh are lower still—0.2% (*Davidson, Davis and Innes*, 1942), and 0.05% (Clark, 1952).

The paucity of reliable data on this type of anaemia is due mainly to difficulties in diagnosis which is usually made on morphological grounds viz. the identification of megaloblasts, transitional megaloblasts or giant metamyelocytes. As these are seen in ordinary blood films in only a minority of cases, marrow biopsy has become the usual diagnostic technique. There is, however, this other approach to the problem viz. the microscopical examination of the buffy coat from the haematocrit in which such cells are concentrated in these cases.

It is not my intention now to discuss the relative merits of various diagnostic procedures—I mention them to emphasise the difficulties in attempting to assess the frequency of gestational megaloblastic anaemia. Nevertheless, I have found that whereas only one case in four can be diagnosed with certainty on the ordinary blood film, three in four can be diagnosed on the buffy coat, while in severe cases with a fully developed megaloblastic change in the marrow it is seldom that the buffy coat fails to give a diagnostic picture. Admittedly border-line cases occur, and in Dundee we reserve marrow biopsy for them.

Before leaving the subject of the buffy coat, however, I would like to draw your attention to a phenomenon which is quite frequently seen in cases of megaloblastic anaemia of pregnancy viz. the occurrence of excessive erythrophagocytosis. Some severe cases, in fact, show a tangled mass of leucocytes, red corpuscles and nuclear debris—not unlike the lupus erythematosus phenomenon, or the masses which may cause micro-embolism in cases of auto-immune haemolytic anaemia. Such wholesale ingestion of erythrocytes stops quickly after treatment with folic acid (*Goodall,* 1955) or folinic acid (*Scott,* 1957) and its intensity contrasts with the less frequent ingestion of small fragments of red cells which occurs in Addisonian pernicious anaemia and other anaemias responding to cyanocobalamin.

This phenomenon, erythrophagocytosis, is of interest as evidence of the lytic element in megaloblastic anaemia of pregnancy; it may also be of significance in relation to the apparent pre-eclampsia, the hypertension, oedema and albuminuria of many of these patients, because such clinical signs are usually associated with the laboratory finding of erythrophagocytosis, and they too appear to be at least partly corrected by folic acid therapy, even before the haemoglobin and haematocrit have risen. It would seem to me that these phenomena are indicative of an alteration of the cell membrane of the erythrocyte and the vascular endothelium, particularly that of the kidney; an alteration which is corrected by folic acid at these various anatomical sites.

These speculations are mainly of academic interest, but the facts are of clinical importance because of the frequency of hypertensive toxaemia in these megaloblastic cases—23% over all; 9% severe; 28% in primiparae; 22% in others. In addition, among normotensive cases 6% had albuminuria plus oedema; 4% had

oedema alone; and 3% albuminuria alone. In sum, then, a total of 36% of cases of megaloblastic anaemia of pregnancy in Dundee had one or more of these three important signs, hypertension, oedema, albuminuria. Yet none of these cases had a fit.

From the point of view of total maternal morbidity these toxaemic megaloblastic cases comprise about 0.5% of all deliveries. Such cases are certainly few compared with the total toxaemia rate of 12%. Yet they benefit so much from folic acid therapy that one ought not to miss them; and with such cases the buffy coat technique seldom fails.

The relationship between the megaloblastic anaemia and toxaemia is rather complex, for while anaemia per se may well be important in the occurrence of oedema and albuminuria, it does, after all tend to lower the diastolic blood pressure and thus to mask a sign of toxaemia. In addition, it is a fact that the severity of the toxaemia is not necessarily related to the depth of the anaemia. While haemoconcentration may explain this in some cases, it is not the whole explanation. Two other possibilities must be entertained: first, that the association between the anaemia and the toxaemia is fortuitous; and, second, that the intensity of megaloblastic change and degree of erythrophagocytic activity are more important in relation to toxaemia than is a low haemoglobin level. The behaviour of some cases supports the first idea; others the second.

Finally, we must raise the question of etiology. This cannot be answered with certainty, but preliminary investigations (*Wilson*, 1959) indicate that a diet more than adequate in calories, high in carbohydrate and low in animal protein is an important factor in the development of this toxaemic megaloblastic anaemia in Dundee. No symposium on pre-eclampsia is complete without reference to this disease.

Summary

As estimated mainly by the buffy coat technique, the crude incidence of gestational megaloblastic anaemia at the maternity department, Dundee Royal Infirmary, is 1.8% of all pregnancies; the corrected incidence is 1.6%. This is high compared with most centres in Britain, but comparisons may be unreliable because of different methods of diagnosis. Hypertensive toxaemia was found in 23% of these cases, and a further 13% had oedema and/or albuminuria. The relationship between these clinical signs and the haematological findings of excessive erythrophagocytosis is discussed. This morbidity may well be related to an unsatisfactory diet.

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