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REVIEW ARTICLE

Maternal Anaemia and Fetal Well-Being*

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ALTHOUGH the paediatrician's practice does not normally start until after the birth of the infant, events during the preceding nine months of the child's life are of great interest and importance to both the obstetrician and the paediatrician. One of the most frequent complications of pregnancy is maternal anaemia, and in the tropics this anaemia may be so severe as to imperil the life of the mother and infant. Fullerton and Turner (1962) have reported a 55 per cent mortality amongst pregnant Nigerian women with packed red cell volume (PCV) 13 per cent or less and with raised jugular venous pressure. The introduction of exchange blood transfusion by these authors, and later the use of ethacrynic acid, a rapidly-acting diuretic, (Harrison, Ajabor and Lawson, 1971) has reduced maternal mortality to about two per cent, but fetal loss still remains high. According to Ojo (1965) and Fleming (1968) total fetal wastage in Nigeria is between 30 and 40 per cent in spite of successful treatment of the mothers with PCV below 23 per cent.

Perinatal mortality from anoxia is directly related to the severity of maternal anaemia, and one third of infants die when the maternal PCV is less than 13 per cent near the time of delivery (Platt, 1970). Fifty per cent of infants in Ibadan have birthweights below 2000g when maternal anaemia (PCV 23 per cent or less) is untreated at the time of delivery (Fleming, 1968). Harrison and Ibeziako (1973) have shown that the birthweight is reduced by about 100g for each two per cent fall in maternal haematocrit if anaemia is uncorrected. How much these fetal complications are the result of anaemia *per se* is not easy to assess, because the anaemia is often of multiple aetiology and is associated with other factors.

There are therefore, three questions which require answers:

1. Anaemia and poor obstetric performance are seen in the same low socio-economic groups and correlations between the two may not imply causation.
2. Pregnancy anaemia is usually easily treated, so that there is a rapidly changing situation in which the effects of the original anaemia may be reversed.
3. The cause of the anaemia, for example, malaria infection, sickle cell disease, chronic renal failure and malnutrition, may have an independent adverse effect on the fetus.

Beta-thalassaemia minor

Pregnancies complicated by beta-thalassaemia minor have been studied in an attempt to isolate maternal anaemia as one factor having an adverse action on the fetus. Beta-thalassaemia minor enables this because, (*i*) patients with thalassaemia minor may be compared to control subjects precisely matched for age, race, parity and economic status, the two groups differing only by the

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presence or absence of a genetically determined anaemia; (*ii*) thalassaemia minor cannot be treated, except by blood transfusion, which is indicated only rarely since the anaemia is usually in a steady state, and (*iii*) beta-thalassaemia minor acts on the fetus through maternal anaemia only, even when it is inherited in the homozygous state by the fetus (Beischer, Holsman and Kitchen, 1968; Fleming and Lynch, 1969; Fleming, 1973).

Beischer, Holsman and Kitchen (1968) studied Italian immigrants in Melbourne, Australia, and found that fourteen per cent of placentas weighed more than 700g when the mother had thalassaemia, compared to seven per cent of the placentas of controls. In a similar group of thalassaemia subjects in Perth, Western Australia, whose haemoglobin (Hb) concentration was in the range 7.2–10.5g per 100 ml there was a highly significant inverse correlation between maternal Hb and placental weight, which was not found in control Italian subjects; the normal correlation between placental weight and birthweight was lost (Fleming, 1973). It is postulated therefore, that even mild maternal anaemia would lead to fetal hypoxia, and that fetal factors in such a situation would stimulate a compensatory placental hypertrophy. This compensation is often inadequate and placental hypofunction may be demonstrated by low urinary oestriol excretion in 25 per cent of pregnant women with Hb below 10.0g per 100 ml (Beischer *et al.*, 1968b).

Reports of actual fetal fate have not been consistent, but they point to the fetus being under stress. A high incidence of abortion, perinatal mortality, premature delivery and low birthweight has been reported from Italy (Lenzi and Lucci, 1957). The Australian experience has been somewhat different; Hocking and Ibbotson (1966) reported twice the usual incidence of fetal distress during labour; Beischer, Holsman and Kitchen, (1968) found three per cent stillbirths as compared to 1.8 per cent in a control hospital population; in Perth, nearly 20 per cent of infants born to mothers with thalassaemia had Apgar scores (Apgar *et al.*, 1958) of three or less, compared to 3.7 per cent in control Italians (Fleming, 1973).

These studies of beta-thalassaemia minor have identified maternal anaemia as the only known cause for changes in the feto-placental unit to the exclusion of other consequences of low socio-economic state and coincidental factors. The studies further show that when there is maternal anaemia throughout pregnancy, there is a compensatory placental hypertrophy, which is not wholly adequate for about 20 per cent of infants when the maternal Hb is in the range of 7.5 to 10.5g per 100 ml and the infants are at an increasing risk as anaemia becomes more profound.

Treated maternal anaemia

In Perth, a study of 331 subjects whose pregnancies were not complicated by haemorrhage, twin pregnancy or beta-thalassaemia minor, has shown that 14.5 per cent of the subjects are anaemic (Hb. < 11.0g per 100 ml) according to the World Health Organization definition (1972), the anaemia being due to iron deficiency in most cases. All the subjects studied received iron and folic acid, and the anaemia usually responded to this therapeutic measure. In this particular study, as in many others, no correlations could be found between maternal Hb iron and folate status on the one hand, and fetal well-being on the other. This was certainly because correction of anaemia, if early enough, reversed the changes in the feto-placental unit; the urinary oestriol values also increased as maternal Hb rose (Beischer *et al.*, 1968b), and fetal development progressed satisfactorily so that birthweight was normal or approaching normal (Fleming, 1968; Harrison and Ibeziako, 1973). In the same study, it was noticed that the birthweight tended to be high when the maternal Hb was low in early pregnancy, and this might be explained by the compensatory placental hypertrophy persisting long after the correction of the maternal anaemia and fetal hypoxia.

If the maternal Hb remained below 11.0g per 100 ml towards the end of pregnancy, there was low urinary oestrogen excretion and placental hypertrophy. Two sub-groups of patients in whom

haematological values have particular bearing on fetal well-being emerged from the overall study:

(*a*) those with recurrent and persistent anaemia and

(*b*) those with renal disease.

Sub-group (a): Recurrent or persistent iron deficiency anaemia

About 10 per cent of the whole group in the Perth study gave a history of anaemia in previous pregnancies and had an iron deficiency anaemia which persisted throughout the study pregnancy in spite of oral iron therapy. In this sub-group, the number of previous abortions correlated negatively with the mean corpuscular haemoglobin concentration (MCHC) and Hb at delivery, and positively with the degree of hypochromia in the study pregnancy. The mean PCV was two per cent lower, and the mean birthweight nearly 250g lower ($P < 0.001$) than in those without previous anaemia. This was somewhat in agreement with the findings in Ibadan by Harrison and Ibeziako (1973), who studied more severe anaemias of different aetiology (malarial haemolysis and folate deficiency). These workers also found that in uncorrected anaemia, each two per cent fall in maternal PCV reduced the birthweight by about 100g.

It is therefore concluded that if treatable anaemia exists at the time of conception, and the anaemia is allowed to persist, the same action on the fetus (increased tendency to abortion, premature delivery and low birthweight) would occur as in maternal thalassaemia minor. Not all these complications may be attributed to anaemia alone in this mixed group of patients, but there is no evidence that maternal iron deficiency has any adverse effect on the fetus except through persistent maternal anaemia.

Sub-group (b): Renal disease

Breidahl *et al.*, (1972) showed that it was the severity of renal tract abnormality underlying bacteriuria in pregnancy which determined the development of anaemia, while Ratten and Beischer (1972) reported that chronic renal disease, although accounting for only seven per cent of all anaemias in Melbourne (Australia), was the most important cause of anaemia in terms of maternal morbidity. In the 54 women in our study who had significant bacteriuria, it was found that the mean Hb was nearly 0.5g per 100 ml lower, and the abnormalities of the peripheral blood (low MCHC, hypochromia and poikilocytosis) were associated with a significant tendency to premature delivery and low birthweight (Fleming, Martin and Stenhouse, unpublished). Therefore, not only should renal function be tested during pregnancies complicated by severe or unresponsive anaemia (Ratten and Beischer, 1972), but also the blood picture may be used in assessing pregnancies complicated by renal disease.

Folate deficiency

Rothman (1970) has reviewed the literature supporting or opposing the hypothesis that folate deficiency in early pregnancy disturbs growth at the uteroplacental site, with subsequent abortion or placental separation and antepartum haemorrhage.

The incidence of megaloblastic erythropoiesis by the end of pregnancy without folate supplements was 18 per cent in one of our studies in Perth. In our other study quoted above, all patients had their folate status assessed by peripheral blood film examination and bioassay of serum and red cell folate; all were then given iron and folate supplements. Sixteen patients subsequently aborted, ten had antepartum and fourteen had postpartum haemorrhages. The initial folate status of the patients who later had uterine haemorrhage did not differ from that of the 331 control patients (Fleming, Martin and Stenhouse, unpublished). These results are in agreement with those obtained by Hall (1972*b*). In addition, a retrospective study of 151 patients with abortion and of 15 others with antepartum haemorrhage provided no evidence that folate deficiency played any role in the aetiology of threatened or inevitable abortion,

abruptio placentae or other forms of antepartum haemorrhage. Similarly, our prospective study and that of Hall (1972 *a*) did not support the view that maternal folate deficiency was a cause of congenital malformation, although this is true of the administration of folate-antagonists (Powell, 1971). It is therefore concluded that folate deficiency in pregnancy causes fetal complications only when there is maternal anaemia.

Malaria

Acquired immunity to malaria infection, in particular *Plasmodium falciparum* in endemic areas, is diminished during pregnancy, especially in the first pregnancy (Gilles *et al.*, 1969); haemolysis leads to anaemia, which develops between 16 and 24 weeks of gestation, and this may become profound, especially if complicated by folate deficiency (Fleming, 1968).

Malaria also affects the fetus adversely through several mechanisms besides maternal anaemia. High fever from any cause would lead to abortion or premature labour; the placenta may be infected, impairing fetal nutrition; congenital malaria may follow, though this is rare if the mother is indigenous to a malarial area (Morley, Woodland and Cuthbertson, 1964; Jelliffe, 1968; Gilles *et al.*, 1969; Hamilton *et al.*, 1972; Harrison and Ibeziako, 1973). Infected placentas are also associated with a mean birthweight which is over 250g lower than in infants of non-infected mothers (Jelliffe, 1968).

The administration of prophylactic antimalarials is the most important single antenatal measure, both for the mother and for the infant, in areas where malaria is endemic (Fleming, Hendrickse and Allan, 1968; Gilles *et al.*, 1969). By this simple and cheap prophylactic measure, maternal fever, haemolysis and anaemia are prevented; folate requirements are reduced; the incidence of abortion and premature labour is diminished, and the mean birthweight increased.

Haemoglobpinoathies

Sickle cell trait

The inheritance of sickle cell trait (Hb AS) is not accompanied by anaemia, and the majority of pregnancies coinciding with this condition are uncomplicated. There are, however, some disadvantages. Sickling of red cells may occur in the renal medulla, leading to scarring and a predisposition to infection. Nearly 14 per cent of pregnant women with Hb AS in America were found to have significant bacteriuria, compared to 6.4 per cent in a control pregnant Negro group. Nearly half of the women with bacteriuria subsequently developed pyelonephritis (Whalley, Martin and Pritchard, 1964). Such patients, comprising about 7 per cent of pregnant women with Hb AS, may be expected to show the fetal complications of maternal renal disease as described above.

Sickle cell trait offers some protection against the effects of malaria in children before they acquire immunity, and a similar advantage has been described in pregnancy. Only 19 per cent of severely anaemic pregnant women in Ibadan had Hb AS, where the expected incidence was 25 per cent; this under-representation of Hb AS was confined to those anaemias with gross splenomegaly, of whom only 7 per cent had sickle cell trait (Fleming, Allan and Stenhouse, 1968). However, the effects will be worse on the fetus once maternal anaemia does develop as there was an over-representation of Hb AS (31.6 per cent) in mothers whose infants suffered anoxic deaths (Platt, 1971). Sickle cell trait combined with the congenital persistence of Hb F (Hb SF) and Hb SD probably have the same advantages and disadvantages as Hb AS.

Sickle cell anaemia (Hb SS)

The severity of complications of sickle cell anaemia in pregnancy are greatly reduced by the use of prophylactic antimalarials, folic acid supplement and other supportive measures. In spite of proper antenatal care, maternal mortality remains over 10 per cent per pregnancy and fetal

wastage about 40 per cent in both Africa and America (Hendrickse *et al.*, 1972*a;* Necheles, 1973). Birthweight in those surviving is low, but not necessarily much lower than accounted for by persistent anaemia (Harrison and Ibeziako, 1973).

Haemoglobin SC disease

Hb SC is the commonest haemoglobinopathy causing complications in pregnancy in West Africa south and west of the river Niger. About one in seventy babies born has homozygous Hb S and one in three hundred and twenty has Hb SC in Ibadan, but relatively few women with homozygous Hb S live or become pregnant, whereas Hb SC carries less morbidity and little mortality in childhood and non-pregnant adults. Hb SC carries a 7.5 per cent mortality and 30 per cent fetal wastage per pregnancy in spite of antenatal care and management of delivery (Fullerton, Hendrickse and Watson-Williams, 1965; Necheles, 1973).

Sickle cell—beta-thalassaemia

Hb.S/thalassaemia is a less morbid condition than sickle cell anaemia or Hb SC disease. Maternal mortality is low and fetal wastage is in the order of 19 per cent (Hendrickse *et al.*, 1972 *b;* Necheles, 1973).

Haemoglobin CC disease and other non-sickling haemoglobinopathies

The morbidity of non-sickling haemoglobinopathies is the result of the degree of anaemia only and there are no complications from infarction. Anaemia may be profound if pregnancy is complicated by folate deficiency or infection. Fetal wastage and birthweight will depend on maternal Hb concentration, as in other anaemias (Hendrickse *et al.*, 1972 *b;* Necheles, 1973).

Conclusions

Maternal anaemia results in fetal hypoxia, and fetal factors cause a compensatory placental hypertrophy, which is often inadequate, as shown by low urinary oestrogen excretion. The Apgar score is 3 or below in about 20 per cent of infants if the maternal Hb is persistently in the range 7.5–10.5 g per 100 ml throughout pregnancy. Fetal complications increase as maternal anaemia becomes more profound, and there is a one-third perinatal mortality when maternal Hb is below 4 g per 100 ml. Birthweight declines about 100 g for each 2 per cent fall of maternal haematocrit if the anaemia is untreated.

Successful treatment of anaemia results in rapid reversal of fetal morbidity, and no correlation may be found between maternal haematology and fetal well-being in the great majority of women attending antenatal clinics.

Maternal renal disease, malaria and sickle cell disease and its variants have actions directly adverse to the fetus in addition to the effects of anaemia. There is no evidence that iron or folate deficiency acts against the fetal well-being except through causing maternal anaemia.

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