The Consequences of Anaemia in Pregnancy

A response to David Rush, *Nutrition and maternal mortality in the developing world* (September 23, 1997).

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To appreciate the morbidity and mortality resulting directly from anaemia, it is necessary to review the pathophysiology of anaemia, (Sharpey-Schafer, 1945; Beet, 1956; Varat *et al*, 1972; Bellingham, 1974; Weatherall, 1996) and to read again articles published between about 1945 and 1970, when meaningful data were collected in developing countries and before appropriate blood transfusion had been introduced.

Pathophysiology of anaemia

Anaemia progresses through three stages, of increasing severity, (i) compensated anaemia, (ii) decompensated anaemia, and (iii) anaemic heart failure. The severity of anaemia does not depend only on the haemoglobin (Hb) concentration, but also on (i) the age of the subject, the young being better able to compensate, (ii) the rapidity of development of anaemia, compensatory mechanisms being more effective in insiduously developing anaemias (eg, aplastic anaemia) and chronic anaemias (eg, sickle-cell disease), and (iii) plasma volume expansion, which occurs in pregnancy (especially multiple pregnancy) and with splenomegaly, and which increases the risk of circulatory congestion and cardiac failure (Harrison, 1967, 1970).

Nonetheless, it is convenient often to classify anaemias according to the Hb levels: decompensation is usual with Hb <70g/l, and anaemic heart failure is unusual with Hb>40g/l.

Stage of compensation

Anaemia stimulates the production of red cell 2,3 - diphosphoglycerate (2,3DPG), which has the properties of fixing Hb in the deoxygenated state, shifting to the right the Hb-oxygen dissociation curve, and enhancing oxygen extraction from Hb by the tissues by as much as 40% (Bellingham, 1974). There is an exaggerated rise of cardiac output in response to exercise, but this a minor compensatory mechanism in the maintenance of tissue oxygenation compared to 2,3DPG in mild anaemia.

Plasma volume (PV) expands to replace the missing red cell volume (RCV) and the

total blood volume (TBV) remains unchanged (Harrison, 1967, 1970). There is a redistribution of blood flow, with increased perfusion of the brain, the myocardium and skeletal musculature.

There is a reduced functional reserve, and subjects become breathless on exertion. Tolerance to exercise, and the abilities to work, to earn and to care for children all decline in women as in men (Viteri and Torun, 1974; Florencio, 1981). The effects of mild maternal anaemia on fetal oxygenation will be discussed later.

Stage of decompensation

When the Hb falls below about 70g/l, the major compensatory mechanisms are cardiovascular. Cardiac output is raised even at rest from about 5L/minute to as much as 13L/minute, through there being and increased of myocardial contractility and a greater stroke volume. There is an exaggerated tacchycardia only on exertion. Peripheral vasodilation and reduced viscosity of the blood help to reduce the load on the ventricles.

The TBV and central blood volume are reduced, which increases the risk of shock following acute haemorrhage (Harrison, 1970).

Compensation is inadequate : lactic acid accumulates and patient are breathless even at rest. Because subjects are unable to perform their work, they present for treatment most often in this stage of anaemia in the developing world.

The clinical signs, besides pallor, are those of the cause of the anaemia, and of a hyperdynamic circulation.

Stage of anaemia heart failure

Cardiac output continues to increase with the severity of anaemia, but the heart is performing more work in the face of diminishing oxygenation, until with Hb<30g/l there is no further rise of cardiac output.

Reduced renal blood flow causes retention of sodium. The plasma volume increases and there develop peripheral oedema, ascites, pulmonary oedema, raised jugular venous pressure and hepatomegaly, evidence of incipient or actual left-sided and right-sided cardiac failure. Death may ensue from anaemic heart failure alone. Some patients die without evidence of heart failure, but apparently as a consequence of gross tissue hypoxia. In either case, death is the direct consequence of anaemia, and other complications such as haemorrhage or infection, are not necessary but may be contributory causes of death.

Anaemic heart failure and death

Gelfand (1946) stated that 17% of heart failure in Harare, Zimbabwe was due to anaemia: Davies (1948) found anaemia to be the cause of heart failure in 4% of all subjects submitted to postmortem examination in Uganda. Beet (1956) reported that 14 (6%) of 235 cases of congestive heart failure were due to anaemia in northern Nigeria.

With clear understanding of the pathophysiology of anemia in pregnancy, and the ability to diagnose anaemia and anaemic heart failure, Lawson (1962) ascribed 14 (17%) out of 84 maternal deaths in hospital patients to anaemia in Ibadan, western Nigeria. From 1955 to 1957 in Ibadan, 18 (20%) of 92 pregnant women with haematocrit (Hct) $\leq$ 0.14 died: 17 (55%) of the deaths were among the 31 women who were in congestive cardiac failure (Fullerton and Turner, 1962; Harrison, 1970).

Blood transfusion

The treatment of severe anaemia by the transfusion of red cells went through three phases. Sharpey-Schafer (1945) advocated the transfusion of concentrated red cells, not whole blood, slowly, so as to reduce as far as possible the increase of blood volume and the load on the failing heart. Mortality remained high, as illustrated by the experience at Ibadan. The introduction of exchange blood transfusion for the treatment of severe pregnancy -

related anaemia in Ibadan, avoided any increase in blood volume while raising the Hct and RCV rapidly: mortality was reduced to 4% (Fullerton and Turner, 1962; Harrison, 1969, 1970). Exchange blood transfusion was largely replaced by the introduction of rapidly acting diuretics, ethacrynic acid or frusemide, which were administrated at the time of a straight slow transfusion of two units of packed red cells (Harrison and Lawson, 1966); the main advantages were simplicity and the reduction of numbers of donor units from five to two per transfusion, but there may have been a further reduction of mortality from 4% to 2% (Krishnankutti, 1967; Harrison, 1968, 1970; Harrison *et al,* 1971).

The efficacy of this treatment of severe pregnancy-related anaemia makes it still the emergency treatment of choice. Because it is a specific treatment of anaemia, the dramatic reduction of mortality when blood transfusion is administered to women with Hct less than 0.20 provides convincing evidence that severe anaemia is the main cause of maternal mortality in these women (Harrison and Rossiter, 1985; Harrison, 1988).

The statements that "no study has addressed whether mortality is lower after treatment of anemia" (Rush, p 43, line7/8), and "we also need to understand the pathways by which severe anemia increases risk of death" (Rush, p43 line 32) do not take into account our knowledge of the pathophysiology of anaemia nor of the efficacy of blood transfusion in preventing death.

Severe anaemia, infection and haemorrhage

In 1963, 248 consecutive pregnant or recently delivered women admitted with Hct<0.24 were studied at Ibadan (Fleming, 1968). Of these, 176 (71%) were anaemic as a result of recurrent malaria and/or folate deficiency: 48 (27%) had Hct <0.13 and would have been at high risk of death from anaemia except that exchange blood transfusion was available. The rate of acute infections was actually inversly related to severity of anaemia in pregnant

women (2% with Hct<0.13; 10% with Hct 0.13-0.18;21% with Hct 0.19 - 0.23). Six patients died, three of congestive cardiac failure shortly after admission before exchange blood transfusion could be administered: other causes of death included typhoid (Hct 0.10), hepatic necrosis (Hct 0.08) and peritonitis (Hct 0.17).

A further 43 patients (17%) had haemorrhage as a major cause of anaemia, including 25 with postpartum haemorrhage. This group of patients had also high prevalence of hepatosplenomegaly related to malaria (10/25 with postpartum haemorrhage), infection (10/25 with postpartum haemorrhage) and folate deficiency (14/42). One patient with postpartum haemorrhage died. Although patients with obstetric haemorrhage may show many of the causes of anaemia prevalent in the population, anaemia itself does not increase the prevalence of postpartum haemorrhage. Harrison (1970) reported an incidence of 3 (2.2%) of haemorrhages in 137 anaemic patients (Hct<0.27) delivered vaginally compared to an overall hospital incidence of 108 (2.1%) in 5129 deliveries. Death, however was likely follow haemorrhage in the grossly anaemic patients. Of 93 maternal deaths in Ibadan in women with Hct <0.27 during the years 1957-1968, haemorrhage contributed in 21 (23%) (Harrison, 1970).

It is concluded that infection and haemorrhage are not more frequent in the severely anaemic pregnant women than in all pregnant women, but when they do coincide, there is a high mortality. The majority of women dying did so as the direct consequence of profound anaemia, without infectious or haemorrhagic complications.

Moderate maternal anaemia and the fetus

Maternal anaemia results in fetal hypoxia, as demonstrated by diminished oxygen tension in amniotic fluid (Johnson and Ojo, 1967). One consequence of this is a

compensatory placental hypertrophy, which may be observed in even moderate maternal anaemia (Hb<105g/l) from any cause, with the exception of malaria (Beischer *et al.* 1968a, 1970; Fleming, 1973). The usual correlation between placental weight and birthweight is lost, and is replaced by a negative correlation between maternal Hb (at first antenatal attendance, the lowest Hb recorded during pregnancy, and at delivery) and placental weight (Beischer *et al.* 1970; Fleming 1973). This compensation is inadequate and there follows low urinary oestriol excretion (Beischer *et al*, 1968b), and a negative correlation between Apgar score at birth and the placental weight/birthweight ratio (Fleming, 1973). Percentages of low birthweight and perinatal mortality rise rapidly once the maternal Hct falls below 0.30 in Nigeria (Harrison *et al.* 1985), observations in agreement with the rapid decline of percentage favorable pregnancy outcomes, recorded in Afro Americans with Hct<30 and white Americans with Hct <33 (Garn *et al* , 1981). (This racial difference is possibly related to the high frequency of α-thalassaemia in Africans and persons of African descent, lowering slightly the reference range of normal Hb.)

The fetus has remarkable powers of recovery when maternal anaemia is successfully treated and pregnancy continues. When Nigerian women presented with severe anaemia (Hct <0.24) and delivered soon after admission to hospital, perinatal loss of single infants was 38%; of surviving infants, 50% weighed less than 2000g and 88% less than 2500g at birth. Of comparable women with severe anaemia treated successfully at least 6 weeks before delivery, only 4% lost their infants (all macerated stillbirths) and of surviving infants only 7% weighed less than 2000g and 27% less than 2500g (Fleming, 1968, 1989).

The statements (Rush, page 24) that "there is scanty and inconsistent evidence to implicate moderate anaemia with excess maternal (or infant) mortality (or morbidity)", and "there is no evidence that treatment of anaemia lowers risk of maternal and infant mortality or

morbidity" cannot be easily justified in the light of these observations.

Although moderate anaemia does not seem to make any significant contribution to maternal mortality, the attempts to prevent and treat moderate anaemia should not be given a low priority for the following reasons:

- moderate maternal anaemia may progress to severe anaemia, and this can be rapid in the cases of malaria and folate deficiency;
- women's work capacity is limited in proportion as the Hb declines;
- fetal hypoxia and its consequences are apparent with the most mild maternal anaemia and are of increasing frequency and severity as anaemia develops;
- the adverse consequences on the infant are reversible with successful management of maternal anaemia.

High maternal haemoglobin concentrations

Garn *et al* (1981) were the first to report the association of high maternal Hb or Hct (>0.41) with lower percentage favorable outcomes. (The figures of 0.41 is taken from Figure 2 of Garn *et al*, as being more comprehensive than the number of fetal deaths taken from Figure 1 by Rush p 20, line 17/18.) In Nigeria both maternal mortality and perinatal mortality increased in this range of Hct (Harrison and Rossiter, 1985; Harrison *et al* 1985). In the United Kingdom, there were five to sevenfold increases in preterm delivery and low birthweight if the lowest Hb recorded during pregnancy was >145g/l (Steer *et al*, 1995).

These high Hb and Hct do not reflect an increase of total RCV, but are the result of failure to expand PV, associated with pre-eclampsia/eclampsia or haemoconcentration consequent to dehydration during prolonged labour (Harrison, 1988; Steer *et al*, 1995). The underlying pathology is responsible for the poor outcomes of pregnancy, haemoconcentration and high Hb. There is no evidence that Hb itself is "toxic" at these levels: polycythaemia,

where there is a true enlargement of the RCV, begins to be symptomatic when the Hct is above 0.50.

The action of iron therapy in raising the Hb in "non anaemic" women is the result of these women being iron deficient initially. It has been shown clearly that intramuscular iron does not have a pharmacological action of increasing Hb or the reticulocyte count in iron-sufficient subjects (de Leeuw and Lowenstein, 1966).

The fear that "women without overt anemia who are given oral iron supplements may have there hemoglobin raised to levels associated with maternal and fetal toxicity" (Rush, p 20), would seem to be unfounded, if the action of iron is to raise Hb within normal physiological limits, and high Hb levels are not causatively related to toxicity. It should be noted that "the increase in hematocrit caused by iron supplementation appears not to have depressed fetal growth" (Rush, p 21), and "increased levels of hemoglobin following iron supplementation are not associated with increased risk of adverse outcome" (Rush p 26).

Excess iron and infection

The claim by Murray *et al* (1978) that iron supplements reactivated malaria and latent microbial diseases in Somali refugees moving south is quoted constantly. At the same time, at the western end of the sahel corridor, Tuaregs migrated south into northern Nigeria, driven by drought; high rates of malaria and other infections were observed in them, but they did not receive iron or other nutritional supplements; their liability to infections was ascribed to exposure to microbes, especially malaria, for which they had no acquired immunity (personal observation): the situation of the Somalis was much the same as that of the Tuaregs. The subject of iron supplementation and infection has been reviewed extensively recently (Gillespie, 1997). It may be concluded that oral iron supplements have minimal or no effect to increase susceptibility to infections.

To be noted is the recent observation that heterozygous inheritance of the common mutation for haemochromatosis has little influence on the iron storage levels of young women (Jackson *et al*, 1998).

Micronutrients and female growth

We observed that iron and/or folate supplements during pregnancy enhanced growth of Nigerian girls who had not yet completed growth (mean growth without supplements 1.11cm, with supplements 2.90cm)(Harrison *et al*, 1985b; Fleming *et al*, 1986). Rush (p32) says "it was not clear whether accelerated growth improved pregnancy outcome". One distinct advantage was the reduction of the need for operations for disproportion to zero in 37 girls receiving folic acid supplements compared to 8 (15%) out of 54 not receiving folic acid ($P<0.01$).

Very rapid growth following folic acid supplements has been observed in another group of subjects; occasionally persons with sickle-cell disease present with severe growth retardation, for example, a bone age of 8 years in adult life; folic acid supplementation is followed by rapid growth which ceases with bone fusion after a few months, and progression to sexual maturity (Watson-Williams, 1962; personal observations).

In the special circumstances of young, short primigravidae who are still growing, supplementation was associated with a decrease of obstructed labour, which does not support the proposal that they "should be absolutely excluded from protein-calorie or other supplementation programs" (Rush, p44).

Fetal growth

In small women whose growth and pelvic development are completed, any increase of fetal size through nutritional supplementation presents a theoretical possibility of raising the risk of obstructed labour. Has this been demonstrated? Has an increase of head

circumference, which is a critical measurement, been shown to follow supplementation, other than in one report on zinc supplements?

HIV, anaemia and maternal mortality

The pattern of anaemia in tropical Africa has been transformed in hospital practice during the past decade. About 70% of persons with AIDS are anaemic: mechanisms are multiple and include:

- the anaemia of chronic disorders secondary to complicating infections (eg tuberculosis);
- infection by parvovirus B19;
- direct action of HIV on erythroid precursor cells;
- disturbed balance of cytokines and growth factors;
- haemolysis;
- nutritional deficiencies of folate, vitamin B_{12}, vitamin A and pyridoxine;
- toxic actions of therapeutic antifolates, antivirals and antineoplastic agents.

Seroprevalence amongst pregnant women is often in excess of 30%, and amongst hospital in-patients over 70%. In the Teaching Hospital of Lusaka during 1995-1997, 10 to 15 blood films from adults with Hb <60g/l were examined daily : in almost all the red cells showed the normochromic normocytic pattern of anaemia secondary to infection. The probability of dying between the age of 15 and 60 in Lusaka is 778 per 1000, which is unprecidentedly high for contemporary African populations (Kelly *et al*, 1998). Two recent publications can be considered against this background.

The study of Zucker *et al* (1994) in western Kenya was primarily into the effectiveness of blood transfusion in the treatment of anaemia in women of reproductive age admitted to hospital, of whom 68% were pregnant or recently delivered. Mortality was

82/2986 (2.75%). Only 27 (33%) out of 82 deaths were pregnancy - related; six maternal deaths were among 73 pregnant or recently delivered women with severe anaemia (Hb<60g/l) (Rush, p14). The attributable mortality in all women due to HIV was 75% and to severe anaemia 31%.

In a prospective assessment of mortality among pregnant women in rural Malawi, estimated maternal mortality rate was 370/100 000 pregnancies and non-maternal mortality (deaths between 3 and 10 months after delivery) was 341/100 000 (McDermott *et al*, 1996). Major contributors to non-maternal deaths were HIV(OR=30.8; 95% CI=7.5-126.8) and severe anaemia (Hct<0.25) (OR=9.9; CI=2.3-42.5).

In conclusion, HIV is now the commonest cause of death of African women of reproductive age, anaemia is frequently due to HIV and contributes to the morbidity and mortality of AIDS, and blood transfusion is often ineffective in saving the lives of anaemic women.

Conclusions

1. Profound anaemia was a common cause of maternal death in developing countries before the introduction of appropriate techniques for blood transfusion. Death from anaemia is certainly still occuring in communities beyond the reach of medical and blood transfusion services (Hoestermann *et al.* 1996), and these deaths are likely to be increasing following economic regression, greater poverty, collapsing health structures and inability or unwillingness of women to attend modern medicine facilities when fees are charged.

2. Moderate anaemia in pregnancy should be prevented for the benefit of the infants, the mothers, the family and the community.

3. Common causes of anemia in pregnancy need to be determined in research studies on samples from the community, and the efficacy of interventions tested. From results,

recommendation can be made as to a "package" of antenatal interventions, which would include supplementation and (where approprate) antimalarials and antihelminthics.

4. Antenatal prevention of anaemia, including the delivery of the "package", should be incorporated into national programmes of health care delivery. The four functions of prevention, diagnosis, treatment and referral, should be defined for the different levels of health care, that is community, primary health care post, district hospital, provincial hospital and referral hospital, following models similar to that in Appendix 8 of WHO (1989).

5. Mortality of women in the reproductive age range in subSaharan Africa is now predominantly related to HIV-infection. AIDS is a frequent cause of severe anaemia, and the most common amongst adult patients admitted to hospital. The effectiveness of programmes to prevent anaemia is likely to be diminished in communities with high HIV prevalence. Nevertheless, such programmes remain important, and could contribute to the prevention of transmission of HIV through blood transfusion.

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