Changes in haemoglobin levels in infants in Malawi: effect of low birth weight and fetal anaemia

S le Cessie, F H Verhoeff, G Mengistie, P Kazembe, R Broadhead, B J Brabin

Methods: A stratified cohort of infants in Malawi (83 with LBW (< 2500 g), 111 with FA (cord Hb < 125 g/l), 31 with both LBW and FA, and 176 controls) was followed during infancy. Hb levels were measured at about 2, 4, 6, 9, and 12 months of age. Repeated measures models were used to describe the changes in Hb levels over time.

Results: The mean Hb concentration in the control group was 95.5 g/l (95% confidence interval (CI) 92.5 to 98.5) at 2 months, 86.9 g/l (95% CI 84.4 to 89.4) at 9 months, and 898 g/l (95% CI 874 to 92.2) at 12 months. Differences between LBW infants and controls increased over time (difference at 12 months: 5.5 g/l [95% CI 1.3 to 9.7]). Infants with FA had borderline significantly lower Hb at 2 months (p = 0.07), but at 6 months their levels were similar to those of controls. The LBW infants and those with FA had the lowest Hb levels (difference from controls at 12 months 7.9 g/l). Parity, placental and maternal malaria at delivery, and sex significantly affected Hb levels after adjustment for LBW and FA. After iron supplementation, Hb significantly increased.

Conclusions: Antimalarial control and iron supplementation throughout pregnancy should be increased to reduce the incidence of infant anaemia and improve child development and survival.

The World Health Organization (WHO) has estimated that in developing countries over 50% of children less than 4 years of age are anaemic. Iron deficiency is probably the most important cause but other nutrient deficiencies, malaria, intestinal parasitic infections, and chronic infections such as HIV also play a role. In malaria endemic countries, severe anaemia in infancy is common. In a study in Southern Malawi, one in four infants had a packed cell volume below 25% two months after birth, and in a cohort study in Tanzania, more than 30% of infants had a packed cell volume below 25% at six months after birth.

Severe anaemia in childhood is a life threatening condition and an important cause of hospital admission in many developing countries. In Malawi in 1990, one in eight inpatient paediatric deaths were related to anaemia. Impaired mental and motor development of young children is associated with iron deficiency anaemia. If anaemia is detected at an early stage, it can be treated with iron supplementation and malaria chemoprophylaxis. However, severe anaemia may require blood transfusions, which are expensive and may have serious risks for the child.

Low birth weight (LBW), which is related to limited iron stores at birth, is a further known risk factor for childhood anaemia. It is not known if fetal anaemia (FA), or low cord haemoglobin (Hb), is an additional risk factor. FA is common in malarious areas, but is less common in non-malarious areas, unless maternal anaemia is severe.

In this paper, the results of an infant cohort study in Southern Malawi are described. The main objective was to examine the effect of LBW and FA on Hb patterns in infancy. The additional contribution of other risk factors known at birth, including maternal health, obstetric history, and gestational age, are studied. Furthermore the effect of iron supplementation during infancy on Hb level is examined.

Methods
Study site and population

This study was undertaken between March 1993 and September 1995 in the two hospitals of Chikwawa District, Southern Malawi. In this rural area, small scale production of maize, sorghum, cotton, and sugar cane are the primary sources of food and income. Malaria transmission is holoendemic, and the prevalence of HIV seropositivity in women is high (25%). Chikwawa District Hospital, one of the two study hospitals, is a government hospital with free services, and Montfort Hospital is a fee paying mission hospital located 30 km south of Chikwawa District Hospital.

Enrolment

All women attending the antenatal facilities of Chikwawa District Hospital or Montfort Hospital between March 1993 and June 1994 were screened at their first antenatal visit (booking) after verbal informed consent had been obtained. A questionnaire was completed by a project nurse, which included information on maternal age and obstetric history. At Chikwawa District Hospital, women received one treatment dose of sulfadoxine/pyrimethamine, according to Malawi government policy, at the first antenatal visit occurring after 18 weeks gestation (“if quickening had occurred”) and a second dose between 28 and 34 weeks gestation. In Montfort Hospital, malaria treatment was based on positive malaria slides collected at booking or when symptoms occurred later in pregnancy.

Delivery

Information on delivery was collected from women who attended the hospital facilities for delivery. For logistic reasons, it was not possible to obtain this information for home or health centre deliveries. Information on the number of antenatal visits and antimalarial drug use during pregnancy was taken from the antenatal card.

The baby was weighed immediately after birth on a Salter scale to the nearest 10 g. Gestational age was assessed...
between 6 and 24 hours post partum using a modified Ballard method.\textsuperscript{26}

**Infant follow up**

A stratified sample of singleton infants was selected, consisting of LBW babies (< 2500 g), infants with FA (cord Hb < 125 g/l), and an equally sized sample of infants with normal birth weight and cord Hb to act as a control group. To control for seasonal factors, babies were enrolled in the follow up study throughout a one year period. Mothers were asked to return to the clinic once a month. An active surveillance system was in place to enable optimum information collection on life status of the child. Hb levels were scheduled to be measured for all infants at about 2, 4, 6, 9, and 12 months of age; extra measurements were taken if necessary for clinical reasons. Conforming to hospital policy, iron supplementation (ferrous sulphate 12 mg/ml; 5 ml twice daily) was prescribed for 30 days if the Hb level was < 80 g/l. Hospital staff remained responsible for treatment, and sometimes iron supplementation was prescribed at higher Hb levels.

**Laboratory investigations**

A blood sample was collected by venepuncture from all women at the first antenatal visit and before delivery, from the cord and placenta, and from the child by a heel or finger prick. Hb level was measured photometrically after conversion into cyanomethaemoglobin using a haemoglobinometer (Biotron, Harrogate, Yorkshire, UK), and packed cell volume was measured by microhaematocrit. The mean of duplicate measurements were taken if necessary for clinical reasons. Conforming to hospital policy, iron supplementation (ferrous sulphate 12 mg/ml; 5 ml twice daily) was prescribed for 30 days if the Hb level was < 80 g/l. Hospital staff remained responsible for treatment, and sometimes iron supplementation was prescribed at higher Hb levels.

Malaria slides were made from maternal blood at booking and delivery, and from the placenta, from blood collected deep between the placental villi. The slides were stained with Giemsa and read, counting asexual *Plasmodium falciparum* parasites against 200 white blood cells. Malaria slides read in Malawi were checked by an experienced microscopist at the Liverpool School of Tropical Medicine. HIV seropositivity of women was determined using ICE\textsuperscript{\textregistered}HIV-1.O.2 (Murex, Dartford, Kent, UK) with confirmation using VIDAS HIV 1/2 new (bioMérieux, Lyon, France). HIV testing was carried out, after counselling and obtaining informed consent, on maternal sera collected during pregnancy.

### Table 1 Frequency of occurrence for the different risk factors in the four stratification groups

<table>
<thead>
<tr>
<th>Factor</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LBW (n=83)</td>
</tr>
<tr>
<td>Sex (boys)</td>
<td>50.6</td>
</tr>
<tr>
<td>Prematurity</td>
<td>45.8***</td>
</tr>
<tr>
<td>Intrauterine growth retardation</td>
<td>61.4***</td>
</tr>
<tr>
<td>Maternal anaemia at delivery</td>
<td>37.3***</td>
</tr>
<tr>
<td>Maternal malaria at delivery</td>
<td>20.7***</td>
</tr>
<tr>
<td>Maternal malaria at recruitment</td>
<td>24.7</td>
</tr>
<tr>
<td>Placental malaria</td>
<td>28.9</td>
</tr>
<tr>
<td>Parity (primipara)</td>
<td>22.9</td>
</tr>
<tr>
<td>HIV mother</td>
<td>42.2*</td>
</tr>
<tr>
<td>High placental parasite density†</td>
<td>24.7</td>
</tr>
<tr>
<td>High delivery parasite density‡</td>
<td>5.3</td>
</tr>
<tr>
<td>One dose of sulfadoxine/ pyrimethamine§</td>
<td>57.9</td>
</tr>
</tbody>
</table>

\(p<0.05, \ *p<0.01, \ **p<0.001, \ compared \ with \ controls.\)

\(\text{Data available for only 85 infants.}\)

\(\text{Data available for only 110 infants.}\)

\(\text{Compared with two doses, only in Chikwawa District Hospital.}\)

LBW, Low birth weight; FA, fetal anaemia.
Ethical approval
The study was granted ethical approval by the Malawi Health Science and Research Committee.

RESULTS
Study sample
At the first antenatal visit, 4104 pregnant women were enrolled in the study, 1523 (37.1%) of whom delivered at either hospital. Multiple births were observed in 43 cases, and 1480 mothers gave birth to a singleton. Stillbirth occurred in 55 cases (3.7%), and neonatal death in the first 48 hours post partum in 24 (1.7%) babies. In liveborn singleton babies, LBW was observed in 211 (14.9%), and 306 (23.3%) had a cord Hb level of less than 125 g/l; 52 of these babies were also LBW. LBW was observed in 211 (14.9%), and 306 (23.3%) had a cord Hb level of less than 125 g/l; 52 of these babies were also LBW. At delivery, 451 mothers consented to participate in the infant follow up study, and 60 refused. Of the infants in the follow up study, three died in the first month post partum, 35 died later in their first year, and 87 were lost during follow up. There were 92 LBW infants, 120 with FA, 32 infants with both LBW and FA, 188 controls, and 19 with either birth weight or FA status unknown.

Twenty two infants had no Hb measurements during follow up. From the other 429 infants, a total of 2138 Hb measurements were taken during the first year of life. Of these, 262 measurements were taken after iron prescription. Of the 429 infants with any Hb measurement, four did not have any measurement at the predetermined time points, six had only measurements after iron supplementation, and, for 18, the birth weight or FA status was not known. Removing these data yields a dataset of 401 infants with 1241 measurements. Of these infants, 83 had LBW, 111 had FA, 31 had both LBW and FA, and 176 were controls. The number of Hb measurements before iron supplementation varied from one to five, with a mean of 3.1.

Description of risk factors measured at birth
Table 1 gives the occurrence of the different risk factors in the four stratification groups. The effect of the number of sulfadoxine/pyrimethamine doses was studied only in Chikwawa District Hospital because in this hospital antimalarial control was according to government guidelines. Table 1 shows that LBW infants were more often premature, intrauterine growth retarded, and born to primipara than controls. Their mothers were more likely to have moderately severe anaemia, at either the first antenatal visit or delivery. Babies born with FA had borderline significantly lower Hb levels in the first few months than controls (difference at 2 months was 4.4 g/l (95% CI –0.5 to 9.4); p = 0.07), but after six months their levels were similar. At 2 months of age, the mean Hb level of infants with both LBW and FA was 9.7 g/l (95% CI 1.3 to 18.1) lower than that of controls, and this difference remained large over time (7.9 g/l (95% CI 1.1 to 14.9) at 12 months). The Hb concentration of these children was lower than that of infants with only LBW but the difference was not significant, except for a borderline significant difference at 2 months (p = 0.07).

Haemoglobin changes over time in the four stratification groups
The Hb levels measured at the prescheduled visits before iron supplementation ranged from 41 to 200 g/l. Figure 1 gives the mean levels corrected for missing values at the five prescheduled visits. The mean Hb level in the control group was 95.5 g/l (95% confidence interval (CI) 92.5 to 98.5) at 2 months after birth. This decreased to a mean value of 86.9 g/l (95% CI 84.4 to 89.4) at 9 months, after which it increased to 89.8 g/l (95% CI 87.4 to 92.2) at 12 months. The difference in Hb levels between LBW infants and controls was small in the first months, but increased over time. At 12 months the mean Hb of LBW infants was 5.5 g/l (95% CI 1.3 to 9.7) lower than in controls. Infants with FA had borderline significantly lower Hb levels in the first few months than controls (difference at 2 months was 4.4 g/l (95% CI –0.5 to 9.4); p = 0.07), but after six months their levels were similar. At 2 months of age, the mean Hb level of infants with both LBW and FA was 9.7 g/l (95% CI 1.3 to 18.1) lower than that of controls, and this difference remained large over time (7.9 g/l (95% CI 1.1 to 14.9) at 12 months). The Hb concentration of these children was lower than that of infants with only LBW but the difference was not significant, except for a borderline significant difference at 2 months (p = 0.07).

For infants of normal birth weight, an increase in mean Hb occurred after 9 months. In the controls the increase was 2.9 g/l (95% CI –0.2 to 6.0), whereas for the infants with FA and normal birth weight, the increase was 5.8 g/l (95% CI 1.8 to 9.8). This is in contrast with the LBW infants, for whom, regardless of the FA status, the mean Hb level between 9 and 12 months did not increase (decrease for LBW infants was 0.6 g/l (95% CI–4.0 to 5.2), and decrease for LBW+FA infants was 0.5 g/l (95% CI 7.0 to 8.0)).

Table 2: Differences in mean haemoglobin concentration (g/l) with 95% confidence intervals during infant follow up for those factors that contributed significantly to the haemoglobin pattern after adjustment for birth weight and fetal anaemia status

<table>
<thead>
<tr>
<th>Factor</th>
<th>2 months</th>
<th>4 months</th>
<th>6 months</th>
<th>9 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (boys v girls)</td>
<td>–0.6 (–4.7 to 3.5)</td>
<td>–1.0 (–4.2 to 2.1)</td>
<td>–4.1 (–7.5 to –0.8)</td>
<td>–5.2 (–8.6 to –1.9)</td>
<td>–3.8 (–7.0 to –0.6)</td>
</tr>
<tr>
<td>Malaria at delivery (yes v no)</td>
<td>2.0 (–2.5 to 6.5)</td>
<td>0.5 (–3.0 to 5.0)</td>
<td>1.4 (–2.3 to 5.0)</td>
<td>–3.2 (–8.9 to –1.4)</td>
<td>–5.0 (–8.7 to –1.2)</td>
</tr>
<tr>
<td>Placental malaria (yes v no)</td>
<td>–0.1 (–5.1 to 4.8)</td>
<td>–0.4 (–4.3 to 3.4)</td>
<td>–2.4 (–6.4 to 1.5)</td>
<td>–3.6 (–7.9 to 0.3)</td>
<td>–5.4 (–9.3 to –1.5)</td>
</tr>
<tr>
<td>Parity (primi v multipara)</td>
<td>–2.3 (–6.9 to 2.3)</td>
<td>0.7 (–2.8 to 4.4)</td>
<td>1.7 (–1.9 to 5.4)</td>
<td>–4.5 (–8.4 to –0.6)</td>
<td>–4.6 (–8.1 to –1.0)</td>
</tr>
</tbody>
</table>

*p<0.05.
Of the 1241 measurements made, 95.3% were less than 110 g/l (the recommended WHO standard for anaemia in infants older than 6 months), and 22.2% were below 80 g/l. The measurements were compared with the threshold of 2 SDs below the mean value of the population described by Dallman. The threshold values were 90 g/l for infants of 2 months, 95 g/l for infants aged 3–6 months, and 105 g/l for those aged 0.5–1 year. At 2 months of age, more than one in three infants had a Hb level below the threshold (36.1% of LBW infants, 40.0% of infants with FA, 60.0% of infants with LBW+FA, and 39.0% of controls were below the threshold). However, at 9 months of age, more than 90% of the measurements were below the threshold and at 12 months all LBW infants and more than 90% of the infants of normal birth weight had a Hb concentration more than 2 SDs below the reference mean.

Relation between Hb patterns over time and other risk factors in the four stratification groups
We studied the additional effect of maternal and infant factors on Hb levels after adjustment for the effect of birth weight and FA. No significant effect of prematurity, intrauterine growth retardation, malaria at first antenatal visit, anaemia in pregnancy, HIV, or number of sulfadoxine/pyrimethamine treatment doses during pregnancy on the Hb pattern in infancy was observed. Table 2 shows the variables that had a significant effect on mean Hb for the different subcategories of infants at the different time points. The differences between the subcategories are largest at 12 months. At 12 months, boys and infants whose mother had peripheral malaria at delivery, placental malaria, or were primipara had significantly lower Hb levels.

For peripheral malaria at delivery and parity, the interaction term with time was significant (p = 0.01 for malaria at delivery, p = 0.03 for parity), indicating that Hb levels change significantly differently over time for infants with and without the risk factor present. For sex and placental malaria, only the overall mean between the subcategories was significantly different (p = 0.0007 for sex, p = 0.01 for placental malaria). No significant effect of parasite density of maternal and placental blood, studied on a logarithmic scale, on Hb pattern in infancy was observed.

A model to predict which infants are most at risk of low Hb
All factors with a significant effect on Hb were entered in a multiple repeated measurements model, and a backwards selection procedure was performed. Parity was removed from the model, as a result of its strong association with placental malaria and maternal malaria at delivery (48.8% of first born infants had placental malaria and 23.4% of infants born to multigravidae). The other variables remained significant (sex, p = 0.0017; placental malaria, p = 0.087; and the interaction between maternal malaria at delivery and visit number, p = 0.014).

To visualise the impact of this model, predictions for mean Hb levels are given in fig 2 for different groups of infants, ranging from controls with no additional risk factors to infants with all risk factors present. Girls whose mothers did not have peripheral malaria at delivery or placental malaria had, on average, Hb levels above the threshold of 80 g/l. If maternal malaria at delivery was present, at 9 months mean Hb concentration for LBW girls (with and without FA) was just below 80 g/l, and this remained low at 12 months. Boys with mothers who had malaria at delivery and placental malaria had an expected Hb level at 9 months below 80 g/l, regardless of the birth weight status.

Effect of iron supplementation
Iron was prescribed to 110 infants. After one year, 28% of the LBW infants, 29% of the infants with FA, 38% of the infants with both LBW and FA, and 29% of the controls had received iron (estimates from Kaplan-Meier curves). Thirty five infants received more than one iron prescription; the maximum
Figure 3 Difference in mean haemoglobin levels with 95% confidence interval as a function of time since first prescription, for infants who received one or more prescriptions of iron compared with infants of the same age and stratification group who did not receive iron.

In this paper changes in Hb patterns of infants living in a malaria endemic area in rural Malawi are described. As far as we are aware, this is the first cohort study to describe infant Hb patterns in a developing country in relation to birth weight and FA. In all infants, regardless of birth weight or cord Hb level, a decline in Hb was observed in the first six months of life. A similar pattern was described in a malaria endemic area in Tanzania by Kitua et al, who observed a significant decline in packed cell volume before the age of 6 months. This is in contrast with studies from Western populations, which show a decline in Hb concentration in the first 6–8 weeks of life, reaching a nadir at 2–3 months, which is subsequently followed by a rise. The continuing decline in Hb concentration in the infants in our study is possibly the result of an iron deficient diet and chronic infection, including malaria. Similarly to studies from affluent populations, we found that LBW was a significant predictor of anaemia later in infancy. LBW infants have a more rapid rate of postnatal growth and smaller iron stores, which are exhausted at an earlier age. At 12 months, the mean Hb level in the LBW group was 5.5 g/l lower than in the control group, and in the LBW and FA group 7.9 g/l lower. After 9 months, the Hb level of normal birth weight infants increased, whereas that of LBW infants remained low, suggesting an inadequate supply of dietary iron.

The contribution of low cord Hb to infant anaemia was limited to the first months of life, and, after six months, Hb levels of infants born with FA were similar to those of controls. This effect was surprising as iron stores at birth mainly consist of iron from circulating Hb, and serum ferritin levels during early life are considered a useful indication of iron stores. Infants with both FA and LBW had lower Hb levels than those with only LBW, but the differences were not significant.

Additional risk factors after stratification for LBW and FA were found to be sex (girls have higher Hb levels), placental malaria, and malaria of the mother at delivery. The additional effect of these risk factors was small in the first months and increased in the second semester. The effect of placental malaria infection on infant anaemia has been reported by Redd et al in a study also from Malawi. They found that placental malarial infection was the strongest risk factor for an infant having anaemia at about 2 months of age. Also Cornett et al observed a strong association between anaemia at 6 months of age and placental malaria in Southern Cameroon, an association that did not persist at 1 year. What is uncertain is whether this association is due to similar malaria exposure in mothers at delivery and their infants or whether it relates to recrudescing infant malaria or immune sensitisation occurring as a consequence of congenital infection.

The significant effect of sex on Hb concentration was unexpected. We have found only a few papers in which Hb levels in infancy differed between girls and boys. In the United Kingdom, Burman found that girls had a significantly higher Hb concentration, but, as in our study, the differences were small. The largest difference in mean Hb in infancy was found at 6 months when boys had a mean Hb level of 116.9 g/l, whereas girls had a mean level of 119.4 g/l. Emond et al, also in the United Kingdom, found ferritin levels to be positively related to birth weight and lower in boys. This sex effect may be the result of increased growth requirements in infancy in boys compared with girls, resulting in increased depletion of iron stores. In a Danish study of term infants, Michaelsen et al observed lower iron stores in infants with greater growth velocity. However, we should be careful not to overinterpret this sex effect and should await confirmation of this finding from future studies.

We did not study in detail the effect of haemoglobinopathies on Hb level. In a subsample, the gene frequency of sickle cell anaemia (n = 222) and α-thalassaemia (n = 76) was determined. After application of the Hardy-Weinberg principle, the gene frequency of sickle cell was calculated to be 0.11 (HbAS 18.1%; HbSS 2.3%), and that of α-thalassaemia to be 0.29 (41% heterozygous (–α/αα); 8.7% homozygous (–α/–α)).

Children who were prescribed iron had a Hb level that was 16.9 g/l lower at the time of prescription than infants of the same age, birth weight, and FA status. At two to three months after the first iron prescription, their mean level was almost equal to the overall mean level of infants of the same age who did not receive iron. Prescribing iron seems to reduce severe anaemia, an effect also observed in a randomised trial in Tanzania, where infants who received daily iron supplementation for four months had a lower incidence of severe anaemia. An analysis of the cost effectiveness of this intervention in Tanzania and the number of disability adjusted life years saved has been published and supports the inclusion of iron supplementation delivered through immunisation programmes as part of control strategies for child survival.

In this paper we examined the contribution of maternal and birth characteristics to infant anaemia. Our study is one of the first in which the relation between FA and infant anaemia is described and the first in a malaria endemic area. We have carried out a careful protocolled follow up of the infants in our study and have analysed these data, taking into account the possible confounding effect of iron supplementation and missing data. This yields a detailed description of Hb patterns in infancy in a malaria endemic country and the effect of LBW, FA, and other birth characteristics on infant anaemia. An important finding was the increasing effects of LBW and malaria in pregnancy in the second half of infancy.

It is of interest to see how the Hb levels are affected by events occurring after birth, such as malaria infection and infant growth. This will be a topic of further research. Our study confirms the importance of birth weight and malaria in pregnancy on the development of infant anaemia, and shows...
the significance of FA to infant anaemia in the first months of life. Maternal anaemia, the main contributor to FA, can be reduced by maternal iron supplementation. Reducing LBW prevalence and the prevalence of malaria at delivery is essential and requires improved antimalarial control during pregnancy. Thus malaria control should also be effective late in pregnancy, as malaria at delivery was related to both fetal and infant anaemia. Improving antimalarial control and iron supplementation throughout pregnancy should have direct effects on reducing infant anaemia and improving child development and survival.

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Authors’ affiliations

S le Cessie, G Mengistie, Department of Medical Statistics, Leiden University Medical Centre, The Netherlands
F H Verhoeff, Department of Paediatrics, P Kazembe Department of Paediatrics, Lilongwe Central Hospital, Lilongwe, Malawi
R Broadhead, Department of Paediatrics, Queen Elizabeth Central Hospital, Blantyre, Malawi
B J Brabin Emma Kinderziekenhuis, Academic Medical Centre, Amsterdam, The Netherlands and Tropical Child Health Group, Liverpool School of Tropical Medicine, Liverpool, UK

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