Malaria is an important cause of anaemia in primigravidae: evidence from a district hospital in coastal Kenya


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Abstract
A study was undertaken in order to determine the prevalence and aetiology of anaemia in pregnancy in coastal Kenya, so as to establish locally important causes and enable the development of appropriate intervention strategies. 275 women attending the antenatal clinic at Kilifi district hospital, Kenya, were recruited in November 1993. The prevalence of anaemia (haemoglobin [Hb] <11 g/dL) was 75.6%, and the prevalence of severe anaemia (Hb <7g/dL) was 9.8% among all parities; 15.3% of 73 primigravidae were severely anaemic, compared with 7.9% of 202 multigravidae (P=0.007). In primigravidae, malaria infection (Plasmodium falciparum) was strongly associated with moderate and severe anaemia (χ² test for trend, P=0.003). Severe anaemia was more than twice as common in women with peripheral parasitaemia as in those who were aparasitaemic, and parasitaemia was associated with a 2.2-g/dL decrease in mean haemoglobin level (P<0.001). In multigravidae, iron deficiency and hookworm infection were the dominant risk factors for anaemia. Folate deficiency and human immunodeficiency virus infection were not strongly associated with anaemia. It is suggested that an intervention that can effectively reduce malaria infection in primigravidae could have a major impact on the health of these women and their infants.

Keywords: malaria, anaemia, Plasmodium falciparum, pregnancy, iron deficiency, folate, hookworm, human immunodeficiency virus, Kenya

Introduction
Severe anaemia in pregnancy is defined by the World Health Organization as a haemoglobin level of less than 7g/dL (WHO, 1988). It is a major preventable contributor to maternal morbidity and mortality, being associated with a high risk of cardiac failure and shock, and rendering women less able to withstand even moderate blood loss at delivery (LAWSON, 1967). Anaemia in pregnancy causes considerable incapacity to women from tiredness, lassitude, breathlessness, and decreased ability to work (WHO, 1979); it is also associated with adverse perinatal outcomes (BRABIN, 1991).

The aetiology of anaemia in pregnancy is multifactorial, with the prevalence and causes varying considerably in different areas of the world. Causes that have been reported in sub-Saharan Africa are malaria, iron deficiency (often exacerbated by hookworm infestation), folate deficiency, haemoglobinopathies and human immunodeficiency virus (HIV) infection (FLEMING, 1989). Most large scale anaemia prevention programmes have concentrated on iron and folate deficiency, without addressing other potentially important non-nutritional causes of anaemia in pregnancy. What is still not well documented is the relative importance, from a public health point of view, of malaria as a cause of maternal anaemia. We aimed to investigate this by assessing the local prevalence and causes of anaemia and severe anaemia on the Kenyan coast, with a view to determining priorities for preventative strategies.

Materials and Methods
The study was based at Kilifi district hospital, 50 km north of Mombasa, on the coast of Kenya. This area of Kenya has perennial transmission of Plasmodium falciparum with 2 seasonal peaks in prevalence of the principal vectors, Anopheles gambiae and A. funestus, in June–August and during January, coinciding with the 2 rainy seasons. On average, individuals can expect to receive 10 infective bites per person per annum (MBOGO et al., 1995) The time in which the study was conducted was a period of low malaria transmission, at the end of the dry season. The study area and its malaria epidemiology have been described elsewhere (SNOW et al., 1993).

Kilifi district hospital has a busy antenatal clinic with an average of 900 women from a predominantly rural population attending every month. Women attending the antenatal clinic were recruited over a period of 4 weeks in November 1993. All women who participated in the study gave full informed consent. Fifteen women were recruited each day, which included all first attenders, with the remainder being a random selection of repeat attenders. Obstetric and menstrual histories were taken, women were examined to establish gestational age, and a sample of venous blood was collected. A full blood cell count was performed on a model M530 Coulter counter. Thick and thin blood films were prepared for the detection of malaria parasites, using standard Giemsa staining, counting parasites over 200 white cells, and calculating counts per microlitre from the white blood cell count; 100 high-power microscope fields were examined to confirm that a film was negative. Blood was tested for human immunodeficiency virus (HIV) antibody status using the membrane based assay HTVCHER, (Ouai-Diagnostic Systems, France). The testing was anonymous, with the samples being analysed only after all identifying features had been removed, making linkage of the results to individual women impossible. Additional investigations were performed on a random selection of women: 187 women were tested for red cell folate, measured by radioimmunoassay, and 217 for serum ferritin, using Melissa® enzyme-linked immunosorbent assay (Cambridge Life Sciences plc). Stool samples were requested from all the study women, and 251 (91%) returned a stool specimen. Stool microscopy was performed using the McMaster technique with egg counts estimated per gram.

Statistical analysis was carried out using the SPSS computer program. For continuous variables, means of the different groups were compared using regression methods. χ² tests were used to investigate the association between groups of discrete variables.

Results
Characteristics of the study population
Two hundred and seventy-five antenatal clinic attenders were recruited into the study; 2 women refused. Of those recruited, 73 (26.5%) were primigravidae, 155 (56.4%) were gravidity 2–5 and 47 (17.1%) were in their 6th or more pregnancy. Women of all gestational ages
were recruited, ranging from 12 weeks to term, the mean and median gestational age both being 26 weeks. Primigravidae and multigravidae had similar gestational ages at recruitment. The majority of women (82.2%) attended clinic for a routine check, 18.7% because they were sick, and only 1% were referred from peripheral health units. Analysis did not show any association between the reason for attendance and either haemoglobin level or malaria parasitaemia.

Haemoglobin levels

Two hundred and eight women (75.6%) were anaemic and 27 (9.8%) were severely anaemic. Primigravidae had a somewhat higher prevalence of severe anaemia than multigravidae, 15/1% (11/72) compared to 7.9% (16/202) (P=0.07). The approximately U-shaped distribution of severe anaemia in different parity groups (Fig. 1) showed that primigravidae and women in their 6th or more pregnancy had a higher prevalence of severe anaemia.

Malaria

Sixty-five women (23.6%) had P. falciparum in their peripheral blood. Primigravidae had higher rates of parasitaemia (33%) than multigravidae (20%) (P=0.04). When parasitaemia was present, primigravidae tended to have much higher densities of parasites than multigravidae, the geometric mean being 1749 parasites/FL in parasitaemic primigravidae compared to 371 parasites/FL in parasitaemic multigravidae (P<0.001).

Reported fever during the pregnancy was common, with 139 women (51%) giving a history of fever at some time during the pregnancy, of whom 52 (37%) reported having had fever many times. Reported fever was not associated with the presence of either anaemia or malaria parasitaemia.

Malaria and anaemia

In primigravidae, P. falciparum infection was strongly associated with anaemia (Table 1; χ² test for trend, P=0.003) and the mean haemoglobin level was 2.23 g/dL lower in women with parasitaemia than in those without (95% confidence interval [CI] 1.21-3.25, P<0.001). Severe anaemia was more than twice as common in primigravidae with peripheral parasitaemia than in those without, though the difference did not reach statistical significance (rate ratio 2.45, 95% CI 0.83-7.23). In multigravidae, parasitaemia was not significantly associated with anaemia (Table 1; χ² test for trend P=0.62) or severe anaemia (rate ratio 0.91, 95% CI 0.27-3.03), and it was associated with a mean haemoglobin level only 0.29 g/dL lower than in those without parasitaemia (95% CI 0.31-0.89, P=0.34).

Table 1. Maternal haemoglobin in relation to the presence of peripheral P. falciparum parasitaemia

<table>
<thead>
<tr>
<th>No. of subjects</th>
<th>Haemoglobin level (g/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gravida 1</td>
<td></td>
</tr>
<tr>
<td>Parasitaemic</td>
<td>24</td>
</tr>
<tr>
<td>Not parasitaemic</td>
<td>49</td>
</tr>
<tr>
<td>Gravida &gt;1</td>
<td></td>
</tr>
<tr>
<td>Parasitaemic</td>
<td>41</td>
</tr>
<tr>
<td>Not parasitaemic</td>
<td>161</td>
</tr>
</tbody>
</table>

Iron deficiency

One hundred and sixty-three of 217 sera tested had ferritin levels below 17 ng/mL, with only 39 (18%) being in the normal range (12-30 ng/mL) and 15 (6.9%) being above 30 ng/mL. Serum ferritin levels were significantly higher in women with P. falciparum infection, irrespective of parity (P<0.001): of 168 women with no parasitaemia, mean serum ferritin level was 7.03 ng/mL (95% CI 5.78-8.28), compared to the mean level in 55 women with parasitaemia, 26.42 ng/mL (95% CI 17.78-35.06). Women with parasitaemia accounted for 80% of the high serum ferritin levels. Figure 2 shows the distribution of ferritin according to haemoglobin level in women with and without parasitaemia. In women with no parasitaemia, low serum ferritin was associated with a mean haemoglobin level of 9.38 g/dL, compared to 11.02 g/dL in women with normal ferritin values and 9.75 g/dL in those with high ferritin levels (P<0.001). In women with malaria parasitaemia, mean haemoglobin levels in those with high, normal and low serum ferritin levels were 8.64 g/dL, 9.28 g/dL and 8.64 g/dL respectively (P=0.52).

Hookworm

Of the 251 women examined, 188 (74.9%) had hookworm eggs in their stool. There was a large range in hookworm egg counts (40-7000 eggs/g of faeces), with 30% of women with eggs in their stool (22% of women overall) having >1000 eggs/g. The egg counts, haemo-

globin levels and gravidity are shown in Table 2. Women with higher hookworm egg counts were significantly more anaemic, with egg counts tending to be higher in multigravidae. When all gravidities were analysed together, an egg count >1000 eggs/g was associated with a mean haemoglobin value that was 0.79 g/dL lower than that in those with an egg count <1000 eggs/g (P=0.004). In multigravidae the difference was 0.82 g/dL, and in primigravidae 0.75 g/dL.

Table 2. Median hookworm egg counts per gram of faeces

<table>
<thead>
<tr>
<th>Hookworm egg counts (g/dL)</th>
<th>No.</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1000</td>
<td>11</td>
<td>7.10</td>
</tr>
<tr>
<td>40-1000</td>
<td>162</td>
<td>6.10</td>
</tr>
<tr>
<td>&lt;40</td>
<td>77</td>
<td>7.20</td>
</tr>
</tbody>
</table>

*Kruskal-Wallis test.

Folate deficiency

Eight of the 184 women tested (4.3%) had red blood cell folate (RBCF) levels below the normal lower limit (110 ng/mL). Red blood cell folate levels were negatively correlated with haemoglobin level (P=0.02; Table 3). This negative correlation was found in both parasitaemic and non-parasitaemic primigravidae and multigravidae. Parasitaemic women had a higher mean...
Table 3. Mean red blood cell folate levels (ng/mL) in relation to haemoglobin and malaria parasitaemia

<table>
<thead>
<tr>
<th>Haemoglobin level (g/dL)</th>
<th>&gt;11</th>
<th>7-10.9</th>
<th>&lt;7</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>240 (n=46)</td>
<td>265 (n=123)</td>
<td>360 (n=18)</td>
<td>0.02</td>
</tr>
<tr>
<td>Parasitaemic</td>
<td>273 (n=7)</td>
<td>293 (n=30)</td>
<td>340 (n=4)</td>
<td>0.884</td>
</tr>
<tr>
<td>Not parasitaemic</td>
<td>234 (n=39)</td>
<td>256 (n=93)</td>
<td>365 (n=14)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

By contrast, in non-malarious areas, anaemia usually increases as gravidity increases, with primigravidae being the least anaemic group. This is presumably because iron deficiency tends to increase as gravidity increases (Isah et al., 1985).

Several studies have shown that, in areas where malaria is endemic, effective antimalarial chemoprophylaxis started before 24 weeks of gestation prevents the development of severe anaemia in primigravidae.

Fig. 2. Association between serum ferritin and haemoglobin in women with (A) and without (B) peripheral *P. falciparum* parasitaemia.

Discussion

This study confirmed that anaemia is a major problem among pregnant women on the coast of Kenya, primigravidae and grand-multigravidae having the highest prevalence of severe anaemia.

The causes of anaemia were multifactorial. Malaria was the main cause of anaemia and severe anaemia among primigravidae, being associated with a reduction of mean haemoglobin level of more than 2 g/dL.

In areas where malaria is endemic, infection with *P. falciparum* in pregnancy is greatest in primigravidae, with the prevalence and intensity of parasitaemia decreasing with increasing gravidity (McGregor & Smith, 1932; McGregor, 1984; Steketee & Breman, 1988; Greenwood et al., 1989). The reasons why primigravidae have a greater predisposition to *P. falciparum* infection remain uncertain. The importance of malaria as a cause of anaemia in pregnancy in this Kenyan population is supported by the tendency of primigravidae to have more severe anaemia than any other gravidity group. This has been found in other malarious areas (van Dongen & Vant Hof, 1983; Brabin et al., 1990; Jackson, D. J. et al., 1991). By contrast, in non-malarious areas, anaemia usually increases as gravidity increases, with primigravidae being the least anaemic group. This is presumably because iron deficiency tends to increase as gravidity increases (Isah et al., 1985).

HIV infection

Nineteen of the 274 women tested (6.9%) were HIV positive, and 3 (15.8%) of them had severe anaemia compared with 9.4% (24/255) of women with no HIV infection (P=0.41). Six of the women who were HIV positive (31.6%) had malaria parasitaemia compared with 66 (25.5%) of those who were HIV negative (P=0.56).

Despite evidence for its important role in the prevention of severe anaemia in primigravidae, most countries currently lack policies for the delivery of effective antimalarial drugs to pregnant women. This is mainly due to the difficulty in identifying drugs which fulfil the requirements of being safe for the mother and foetus, effective as an antimalarial compound, acceptable to women, and affordable. With increasing chloroquine resistance in many parts of the world, compounded by frequently poor compliance due to its bitter taste, chloroquine prophylaxis is often no longer effective. In Malawi, compliance with a weekly chloroquine regime was only 36%, and its efficacy 8% (Heymann et al., 1990). Daily proguanil may be an effective alternative which was shown to have good compliance in the studies.
HIV infection was detected in 6.9% of the population tested. The proportion of women with malaria or severe anemia was higher in the group of women who were HIV positive, although the association did not reach statistical significance. In Malawi, HIV infection has been shown to be associated with all neonatal parasitaemias (Wirima et al., 1993), and HIV infection has frequently been shown to be associated with anemia (Doukas, 1992).

Conclusion

This population has high prevalences of anemia and severe anemia in pregnancy. Iron deficiency and hookworm were the main factors associated with anemia in multigravidae, whereas in primigravidae malaria parasitaemia was the most important risk factor identified. The prevention of severe anemia could have a major impact on the health of pregnant women and could contribute to a reduction in maternal mortality. There is an urgent need for studies to identify effective means of preventing the severe anemia secondary to malaria infection in pregnancy.

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