HUMAN IMMUNODEFICIENCY VIRUS SEROPOSITIVITY AND MALARIA AS RISK FACTORS FOR THIRD-TRIMESTER ANEMIA IN ASYMPTOMATIC PREGNANT WOMEN IN WESTERN KENYA

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Abstract. To assess risk factors for anemia in late pregnancy, we studied healthy pregnant women with a singleton uncomplicated pregnancy of ≥ 32 weeks attending the prenatal clinic in the Provincial Hospital in Kisumu, Kenya. Between June 1996 and December 1998, 4,608 pregnant women had a blood sample collected for hemoglobin (Hb) measurement, malaria smear, and testing for human immunodeficiency virus (HIV). The mean ± standard deviation of Hb was 9.58 ± 1.8 g/dL; 21% had malaria in their blood; and 25% of the women were HIV seropositive. Plasmodium falciparum parasitemia was more common among HIV-seropositive women in all gravidities compared with HIV-seronegative women (risk ratio, 1.71; 95% confidence interval, 1.53–1.92). In a multivariate analysis, for primi- and secundigravidae women, the factors malaria, belonging to the Luo tribe, and HIV seropositivity were significantly associated with anemia (Hb < 11 g/dL), and HIV seropositivity and documented fever were associated with severe anemia (Hb < 7 g/dL). In women of higher gravidities, HIV seropositivity was the only statistically significant factor associated with any anemia or with severe anemia. Asymptomatic HIV seropositivity is an important risk factor to be considered in the differential diagnosis of maternal anemia, independent of P. falciparum parasitemia.

INTRODUCTION

Anemia in pregnancy is a major public health problem in sub-Saharan Africa, where the prevalence can be as high as 75%. Anemia, even when mild, is associated with reduced work productivity. During pregnancy, severe anemia (hemoglobin [Hb] < 7 g/dL) may result in circulatory changes that are associated with an increased risk of heart failure. During labor, women with severe anemia are less able to endure even moderate blood loss and as a consequence are at a higher risk of requiring a blood transfusion during delivery. In addition, severe anemia in pregnancy is an important direct and indirect cause of maternal death and for the fetus, severe maternal anemia may result in intrauterine growth retardation, stillbirth, and low birth weight.

The etiology of anemia in sub-Saharan Africa is complex and multifactorial. Malaria is reported as a major cause of anemia, particularly in first and second pregnancies. Iron deficiency is the most common cause of anemia related to nutrition and is particularly common in multigravidae women. Other nutritional deficiencies (vitamin B12, folic acid, and vitamin A), congenital blood cell disorders (sickle cell disease, α-thalassemia, and glucose-6-phosphatase deficiency), and infections (hookworm, schistosomiasis, or tuberculosis) may also contribute to anemia in pregnancy.

Although human immunodeficiency virus (HIV) infection is now well recognized as a major problem among pregnant women in sub-Saharan Africa, its impact on maternal health in the absence of acquired immunodeficiency syndrome (AIDS) is not well documented. HIV infection has been associated with anemia in pregnancy and may have both a direct effect on decreasing Hb levels and an indirect effect by increasing malaria. Conversely, iron-deficiency anemia and malaria have been associated with impairment of the immune system and could have an impact on the course of HIV and other infections.

In Kisumu, Kenya, we studied the interaction between malaria and HIV during pregnancy. This study provided an opportunity to focus on risk factors for anemia in pregnancy in an area where both malaria and HIV infection are common.

MATERIAL AND METHODS

Study site. This study was conducted at Nyanza Provincial General Hospital (NPGH) in Kisumu, Kenya, with a population of ~300,000, is located on the shore of Lake Victoria in western Kenya. Malaria transmission occurs throughout the year, with peak transmission typically at the end of the rainy season from mid-April through June. Plasmodium falciparum accounts for 98% of the malaria cases. Chloroquine resistance is widespread, and ~75% of P. falciparum infections demonstrate an Rho-RhII resistance pattern. NPGH is a government-referral hospital with a total of 400 beds; it provides health care mostly to the local low-income population. On average, ~100 women attend the prenatal clinic service daily, of whom 30% arrive for their first prenatal visit.

Study population and enrollment procedures. Healthy pregnant women visiting the prenatal clinic service of the NPGH with an uncomplicated singleton pregnancy of at least 32 weeks’ gestation and residing in the Kisumu area were invited to participate in the study. Women with known underlying chronic illness (e.g., diabetes mellitus or cardiovascular disease), a complication of pregnancy, or an inability to provide informed consent were excluded from participation. After informed consent was obtained, a questionnaire was completed to collect information on age, place of residence, education, socioeconomic status, and medical and obstetrical history. Information was obtained regarding recent hospital admissions, symptoms, and medications. Body weight and axillary temperature were measured. After the
patient received counseling about HIV, blood was obtained by fingerprick for HIV testing, a malaria thick smear, and Hb levels. An appointment was made for posttest counseling. All women, regardless of their HIV testing results, were encouraged to deliver in the hospital. Although iron and folic acid tablets are standard components of prenatal services, during the study period, they were not routinely available. The study was completed before the introduction of presumptive intermittent treatment with sulfadoxine-pyrimethamine as the national policy for control of malaria in pregnancy.

Laboratory procedures. Peripheral blood smears were stained with Giemsa and examined under oil immersion for malaria parasites. A thick smear was considered negative if 100 microscopic fields revealed no parasites. Malaria parasites were counted against 300 leucocytes. Parasite densities were estimated by assuming a count of 8,000 white blood cells per microliter of blood. Hemoglobin was measured with a HemoCue machine (HemoCue AB, Angelholm, Sweden). HIV testing involved the use of 2 rapid test methods: Serostrip HIV-1/2 (Saliva Diagnostic Systems Pte. Ltd., Singapore) and Capillus HIV-1/HIV-2 (Cambridge Diagnostics, Wicklow, Ireland).

Definitions. Anemia was defined as Hb < 11 g/dL; severe anemia was defined as Hb < 7 g/dL. An uncomplicated pregnancy was defined as a pregnancy without evidence of multiple gestation, hypertension, pre-eclampsia, polyhydramnios, an abnormal presentation of the fetus, a history of caesarian section, hemorrhage, or recurrent abortions (>2). Socioeconomic status was based on materials used for house construction. Documented fever was an axillary temperature of ≥37.5°C at the time of screening. Low maternal weight was defined as a maternal body weight of <50 kg. Malaria was defined as the presence of asexual-stage parasites in thick smears, independent of the presence or absence of clinical signs or symptoms and independent of species. HIV seropositivity of adult women was defined as a reactive result on both rapid tests; women not reactive by the Serostrip HIV-1/2 test were considered HIV seronegative. In case of an inconclusive result, a Western blot test was performed. The sequential rapid test algorithm was assessed previously by confirmation with Western blot; the sensitivity, specificity, positive predictive value, and negative predictive value for the combined 2 rapid tests were 99.8%, 98.9%, 99.8%, and 98.9%, respectively (Steketee RW and others, unpublished data). Rainy season included the months April, May, and June (long rains) and October and November (short rains). Grande multigravidae were women who were pregnant for the sixth time or more.

Analysis and statistical methods. Differences in means were compared by Student’s t-test and 1-way analysis of variance. The Mann-Whitney test was used for nonparametric comparison of 2 groups. Differences in proportions were analyzed using the chi-square test or Fisher’s exact test when appropriate. Primi- and secundigravidae women (G1/G2) had many characteristics that were significantly different when all gravidity groups were compared by Student’s t-test and 1-way analysis of variance (Table 1). To assess risk factors for anemia, the analysis was stratified by these gravidity groups (G1/G2, and G≥3). Poisson regression was used to examine the association between anemia and several maternal characteristics that were found to be significant in the univariate analysis, that we thought were biologically important, or both on the basis of published reports. Factors were removed if they were not statistically associated (P < 0.05) with “any anemia” or “severe anemia” after adjustment for other factors. Possible interactions between significant variables were assessed. The statistical programs SPSS (SPSS for Windows

Table 1

Characteristics of the study population

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n = 4,808)</th>
<th>G1 (n = 1,870)</th>
<th>G2 (n = 1,128)</th>
<th>G≥3 (n = 1,810)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years), mean ± SD†</td>
<td>22.1 ± 4.9</td>
<td>18.8 ± 2.5</td>
<td>21.2 ± 3.0</td>
<td>26.6 ± 4.6</td>
</tr>
<tr>
<td>Luo tribe (%)</td>
<td>79.1</td>
<td>79.1</td>
<td>78.9</td>
<td>79.3</td>
</tr>
<tr>
<td>Education ≤ 8 years (%)‡</td>
<td>63.7</td>
<td>70.2</td>
<td>69.3</td>
<td>52.2</td>
</tr>
<tr>
<td>Married (%)§</td>
<td>79.3</td>
<td>56.7</td>
<td>90.2</td>
<td>89.0</td>
</tr>
<tr>
<td>Socioeconomic status (low/middle) (%)¶</td>
<td>79.3</td>
<td>74.1</td>
<td>83.4</td>
<td>82.4</td>
</tr>
<tr>
<td>Reported fever in previous week (%)§§</td>
<td>22.9</td>
<td>22.2</td>
<td>20.3</td>
<td>25.6</td>
</tr>
<tr>
<td>Antimalarials in this pregnancy (%)¶¶</td>
<td>19.5</td>
<td>16.3</td>
<td>17.6</td>
<td>24.7</td>
</tr>
<tr>
<td>Hematins in this pregnancy (%)</td>
<td>11.1</td>
<td>11.4</td>
<td>11.0</td>
<td>10.7</td>
</tr>
<tr>
<td>Hospitalized in this pregnancy</td>
<td>3.1</td>
<td>3.0</td>
<td>3.4</td>
<td>3.2</td>
</tr>
<tr>
<td>Gravidity, median (range)</td>
<td>2 (1–11)</td>
<td>1</td>
<td>2</td>
<td>4 (3–9)</td>
</tr>
<tr>
<td>Weight (kg), mean ± SD¶¶</td>
<td>63.1 ± 8.1</td>
<td>62.6 ± 7.7</td>
<td>62.4 ± 7.5</td>
<td>64.1 ± 8.8</td>
</tr>
<tr>
<td>Temperature ≤ 37.5°C (%)¶¶</td>
<td>2.1</td>
<td>2.8</td>
<td>2.0</td>
<td>1.3</td>
</tr>
<tr>
<td>Malaria parasitemia (%)§§</td>
<td>20.7</td>
<td>27.3</td>
<td>19.0</td>
<td>14.2</td>
</tr>
<tr>
<td>Geometric mean parasite density per microliter of bloods§¶¶</td>
<td>545</td>
<td>758</td>
<td>492</td>
<td>285</td>
</tr>
<tr>
<td>HIV seropositive%*</td>
<td>25.2</td>
<td>22.0</td>
<td>29.0</td>
<td>25.4</td>
</tr>
<tr>
<td>Hemoglobin (g/dL), mean ± SD††</td>
<td>9.58 ± 1.8</td>
<td>9.57 ± 1.7</td>
<td>9.46 ± 1.7</td>
<td>9.68 ± 1.8</td>
</tr>
<tr>
<td>Hemoglobin &lt; 11 g/dL (%)§§</td>
<td>77.8</td>
<td>78.6</td>
<td>80.6</td>
<td>75.0</td>
</tr>
<tr>
<td>Hemoglobin &lt; 7 g/dL (%)¶¶</td>
<td>6.8</td>
<td>6.5</td>
<td>7.8</td>
<td>6.5</td>
</tr>
</tbody>
</table>

* G1 = primigravidae; G2 = secundigravidae; G≥3 = gravidae 3 or more.
† SD = standard deviation.
‡ Between G1 and G2, P < 0.05, and between G2 and G≥3, P < 0.05
§ Between all gravidity groups, P < 0.05
¶ Between G1 and G2, P < 0.05, and between G1 and G≥3, P < 0.05
§§ Between G1 and G2, P = 0.003.
** Results of HIV tests available for 4,517 women.
†† Between G2 and G≥3, P = 0.001.
The prevalence of malaria among G2 was also significantly higher than among multigravid women (RR, 1.34; 95% CI 1.13–1.59). In 98.9% of the infections, *Plasmodium falciparum* was present. HIV-seropositive women were more likely to have malaria parasites than HIV-seronegative women (RR, 1.71; 95% CI, 1.53–1.92) and to have significantly higher geometric mean parasite densities (907 and 408 parasites per microliter of blood, respectively; t-test, *P* < 0.001). In G1 with any anemia, the geometric mean parasite densities was significantly higher compared with G1 with no anemia (t-test: *P* = 0.008), for severe anemia, no significant difference was detected. Women of higher gravidities with anemia did not have significant differences in geometric mean parasite densities compared with those without anemia (data not shown).

Overall, 2.1% of the women had documented fever. The HIV-seropositive women were more likely to have documented fever than were HIV-seronegative women (RR, 2.24; 95% CI, 1.50–3.36). Documented fever was associated with parasitemia among all women of all gravidities (RR, 2.08; 95% CI, 1.64–2.65).

A large proportion of women (44.4%) reported use of medication for fever or malaria in this pregnancy: 1,108 women (54.1%) had used an antipyretic, 999 women (43.9%) had used an antimalarial, and 40 women (2.0%) used an unknown drug. Of the 899 women who reported the use of an antimalarial, 68.5% reported use of chloroquine, 27.5% reported use of sulfadoxine-pyrimethamine, and 4% reported use of quinine. The HIV-seropositive women were more likely to have a history of fever (RR, 1.16; 95% CI, 1.03–1.30), to report the use of antimalarials (RR, 1.18; 95% CI, 1.04–1.35), and to have been hospitalized than were HIV-seronegative women (RR, 1.63; 95% CI, 1.17–2.28).

Only 509 pregnant women (11%) had a history of hematocrit before enrollment into the study; of these, 216 (42.4%) had used both folic acid and iron tablets, 43 women (8.4%) had used folic acid alone, and 250 women (49.1%) had used iron tablets alone. Women with a history of intake of hematocrits were more likely to have a history of fever (RR, 1.36; 95% CI, 1.18–1.57), to have taken antimalarials (RR, 1.88; 95% CI, 1.64–2.16), or to have been admitted in a hospital during this pregnancy (RR, 2.59; 95% CI, 1.71–3.61), but they were not more likely to be HIV infected.

**Risk factors for anemia.** Characteristics associated with any anemia and severe anemia by univariate analysis are shown in Table 3. The factors associated with any anemia in G1/G2 were, in order of the strength of the association: malaria, tribe, HIV seropositivity, documented fever, enrollment during rainy season, and a history of fever; for severe anemia, significant factors included documented fever, HIV seropositivity, tribe, and malaria. The factors associated with any anemia in G=3 included: HIV seropositivity, tribe, an unfinished primary-school education, and malaria. However, HIV seropositivity was the only significant factor for severe anemia for G=3. No significant association was found between severe anemia and marital status, socioeconomic status, fever in the week before the prenatal clinic visit, season of the year, the use of antimalarials or hematocrits in this pregnancy, and low maternal weight.

Among HIV-seronegative G1/G2, reported use of antimalarial treatment in this pregnancy was associated with a significant reduction in parasitemia (RR, 0.69; 95% CI,
DISCUSSION

This study demonstrates that malaria and HIV seropositivity are important, independent risk factors for anemia in pregnancy in Kisumu, Kenya. Anemia is a public health problem here, as it likely is in other places in sub-Saharan Africa where HIV infection and malaria are both common. The prevalence of any anemia in this population of otherwise healthy women was high (77.8%) and similar to that reported from the other studies among pregnant women in coastal Kenya, Zaire, and Tanzania.2–4 However, in this study setting, anemia in pregnancy was significantly higher than previously reported from western Kenya (44.4%) in 1981, as well as from Mozambique (58%) in 1986 and Benin (55%) in 1987.26–28 These lower rates were reported before the spread and intensification of chloroquine-resistant *P. falciparum* parasitism.

The prevalence of severe anemia was significantly higher among HIV-seropositive women for all gravidities (Figure 1), and the relative risk increased with increasing gravidity (G1: RR, 1.48; 95% CI, 1.01–2.16; G2: RR, 1.57; 95% CI, 1.05–2.36; and G≥3: RR, 1.76 95% CI, 1.21–2.58). The prevalence of severe anemia was significantly higher among HIV-seropositive women for all gravidities (Figure 1), and the relative risk increased with increasing gravidity (G1: RR, 1.48; 95% CI, 1.01–2.16; G2: RR, 1.57; 95% CI, 1.05–2.36; and G≥3: RR, 1.76 95% CI, 1.21–2.58).
lower rate of anemia in pregnancy has also been recently reported from Malawi (60.0%), where malaria transmission is lower than in western Kenya and where sulfadoxine-pyrimethamine has replaced chloroquine for prevention of malaria in pregnancy.29

The prevalence of severe anemia (Hb < 7 g/dL) in this study was 6.8%. This was higher than that previously reported in 1991 from Zaire (3.7%) but slightly lower than recent reports from coastal Kenya (9.8%), Tanzania (9.3%), and Malawi (8.3%).2,4,30 In all of these previous studies, G1 had the highest risk for severe anemia.2–4,29 In the current study, women in their second pregnancy were most at risk for severe anemia (7.8%), but differences with the rates in G1 (6.5%) and multigravidae women (6.3%) were not significant. Pregnant women with clinical symptoms of severe anemia would have been excluded from participation in this Kisumu study because only women who were believed to be healthy and who had an uncomplicated pregnancy of at least 32 weeks’ gestation were eligible for enrollment. Thus, the prevalence of severe anemia reported in this study is likely to be an underestimate of the rate in the overall prenatal clinic population.

Our finding that malaria is an important risk factor for anemia among G1 and G2 in Kisumu but not among G≥3 is consistent with other reports from sub-Saharan Africa.2–4 In malaria-endemic areas where adults have acquired a high level of immunity to clinical malaria, women experiencing their first pregnancy, and to a lesser extent their second pregnancy, have an impaired ability to clear malaria parasites from peripheral blood compared with nonpregnant women of the same age.31 With increasing gravidity, the prevalence and density of malaria parasitemia decreases.32,33 Although in our study malaria parasitemia was not associated with severe anemia late in first and second pregnancies, a recent study from coastal Kenya has reported that among G1, treatment and prevention of malaria in pregnancy reduces severe anemia in the third trimester.34

In Kisumu, HIV-seropositive pregnant women were more likely to have positive malaria smears than HIV-seronegative pregnant women. The susceptibility of HIV-seropositive pregnant women to asymptomatic malaria parasitemia has previously been reported from studies in Kenya and Malawi.17,19,25 Unlike the studies in Malawi, where a significant difference in the prevalence of malaria parasitemia was seen in multigravidae women only, in this study, HIV-seropositive women of all gravidities were at increased risk of parasitemia. The higher transmission rates of malaria in Kisumu compared with Malawi may contribute to the observed difference in prevalence of malaria parasitemia in HIV-seropositive pregnant women by gravidity. These differences are not likely to be due to a higher level of HIV-related immunosuppression among pregnant women in Kisumu because only asymptomatic women were eligible to participate, and those with symptomatic HIV-related immunosuppression would have likely been excluded. This is confirmed by the finding that in this same study population in Kisumu, 70% of asymptomatic HIV-seropositive pregnant women had a CD4 count of ≥ 500 cells/µL 1 month postpartum; thus, the increased risk of malaria in HIV-seropositive pregnant women occurs even in the absence of AIDS or severe immunosuppression (Nahlen B, unpublished data).

In first and second pregnancies, HIV seropositivity was an important risk factor for any anemia and severe anemia. Although HIV seropositivity was associated with a higher prevalence of malaria parasitemia in these women, multivariate regression analysis failed to show a significant interaction between malaria parasitemia and HIV seropositivity.
for G1 and G2. This indicates that HIV seropositivity is an important risk factor for maternal anemia independent of malaria and confirms 2 earlier reports from Zaire and Malawi.\textsuperscript{2,9} For women with $\geq 3$ pregnancies, HIV seropositivity was the only risk factor for any anemia and severe anemia that could be identified in this study. Results of the multivariate regression analysis also suggest that the relative impact of HIV on maternal anemia was greater among multigravid women than among women in their first or second pregnancy.

In this study, no information was available on other factors that may contribute to anemia during pregnancy, such as red blood cell disorders and hookworm infection. Because we did not measure iron, folic acid, or vitamin A levels in the Kisumu prenatal clinic population, the contribution of nutritional deficiencies to anemia in late pregnancy cannot be assessed. Iron deficiency is known to be a common cause of anemia in pregnancy and is the most common nutritional deficiency among women in developing countries.\textsuperscript{1,5} Iron supplementation has proven efficacious in reducing anemia in pregnancy, but lack of availability has been a problem.\textsuperscript{35–37} Where vitamin A deficiency is common, vitamin A supplementation has also been shown to enhance the effect of iron supplementation on reduction of anemia in pregnant women.\textsuperscript{38} Iron and folic acid tablets are recommended and provided as part of prenatal care services in Kenya. However, in Kisumu, the actual number of women receiving and taking either of these supplements was low (11%), and less than half of these women had used both iron and folic acid tablets. Thus, in this large prenatal clinic, only 1 of every 20 pregnant women was receiving the recommended doses of iron and folic acid. The prevalence of anemia among women who reported taking iron and folic acid supplements was not less than among women who did not, but no information was available on the dose, length of treatment, and compliance with the supplement regimen. Women with a history of fever or a hospital admission were more likely to have taken iron or folic acid; thus, a beneficial effect of iron and folate on Hb levels would have been obscured if pregnant women mainly took these drugs when they were ill and may have been more likely to be anemic.

Prevention of anemia may be particularly important for HIV-seropositive pregnant women, in whom the value of blood transfusions may be more limited.\textsuperscript{8,39} Associations between blood transfusions, activation of latent viral infections, and a lack of survival benefit have been reported in people infected with HIV.\textsuperscript{9,39} Although studies have reported an association between maternal anemia and vertical transmission of HIV, it is possible that anemia is a marker for more advanced HIV-related immunosuppression and subsequent increased risk of mother-to-infant HIV transmission.\textsuperscript{30–42}

Whether programs to deliver hematinsics and antimalarials in an effort to prevent anemia during pregnancy will be as effective for HIV-seropositive women as for HIV-seronegative women is unknown. The need for more frequent doses of sulfadoxine-pyrimethamine to prevent malaria in HIV-seropositive pregnant women, the concern that iron supplementation may be less useful in the presence of HIV infection, and the reported beneficial effects of multivitamin supplementation among HIV-seropositive pregnant women on T-cell counts points to the need for further evaluation of prevention strategies in areas of high HIV prevalence.\textsuperscript{2,34–44}

This study confirms the importance of anemia in late pregnancy as a common problem in sub-Saharan Africa. In this study, anemia was associated with malaria parasitemia in first and second pregnancies. For all pregnant women, asymptomatic HIV infection was an important additional risk factor to be considered in the differential diagnosis of anemia. There is a need for further assessment of the effectiveness of malaria prevention on reduction of anemia in pregnancy and subsequent improvement in maternal and infant health. Prevention of HIV infection should be given high priority as well; our results indicate that a reduction in HIV prevalence would be expected to have an impact on reducing anemia among all pregnant women as well as other obvious benefits. Increased knowledge of the impact of the routine interventions and assessment if additional interventions, such as provision of multivitamins and treatment for other parasitic infections, should be provided to pregnant women in areas of high HIV prevalence, are also needed.\textsuperscript{45} The low coverage of iron and folate in this prenatal clinic population demonstrates the importance of developing strategies to improve delivery and compliance of routine interventions that have already been shown to reduce anemia in pregnancy.

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