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# EFFECT OF CHLOROQUINE CHEMOPROPHYLAXIS DURING PREGNANCY ON BIRTH WEIGHT: RESULTS OF A RANDOMIZED TRIAL

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*Abstract.* To determine the effect of chloroquine chemoprophylaxis during pregnancy on birth weights, a randomized trial was carried out in 1987 and 1988 in Banfora, Burkina Faso (West Africa). Seven hundred forty-five randomly selected women treated with chloroquine sulfate were compared to with 719 controls who received no treatment. In spite of an unquestionable effect of chloroquine in preventing placental infection (4.1% infected placentas in the treated group versus 19.0% in the controls), the mean difference in birth weights between the two groups (6 g) was not significant. The difference in the proportion of low birth weight (LBW) newborn babies in two groups (16.3% versus 16.4%) was also not significant. However, there was a strong relationship between placental infection and birth weight (the mean birth weight difference between infected and uninfected placentas was 113 g, and the proportion of LBW babies was 26.0% in infected placentas versus 14.8% in uninfected placentas). The small difference in birth weights observed between the two groups may be due to the fact that the prevalence rate of placental infection is low and that prophylaxis is effective only on a portion of the subjects in the treated group. It may also indicate that malaria is only one of several risk factors responsible for LBW. The relatively small increase in birth weight, the expected poor acceptance of mass prophylaxis, and the spreading of chloroquine-resistant *Plasmodium* strains should be considered before extending malaria chemoprophylaxis to all pregnant women. It might be worth considering to limit prophylaxis to primigravidae.

One of the main consequences of malaria in pregnant women that have been described in sub-Saharan Africa is low birth weight among babies born to mothers whose placentas were infected.[1–11] This is one of the reasons that motivated the World Health Organization (WHO) in 1984 to recommend chemoprophylaxis with chloroquine during pregnancy. By lowering the rate of maternal and thus placental infection, one can expect that such a prophylaxis would both increase mean birth weights of the babies born to treated mothers and improve child survival. Although the necessity to evaluate the precise effect of maternal malaria on birth weight has been frequently stressed,[12] no carefully controlled trial of chloroquine prophylaxis has been reported.

In Burkina Faso (West Africa), since chemoprophylaxis was not believed to produce a significant reduction in morbidity and mortality,[13] the only recommendation of the Ministry of Health was chloroquine treatment of febrile episodes. This made it possible to perform a randomized trial in 1987 and 1988 on the impact of chloroquine prophylaxis during pregnancy in the city of Banfora.

## MATERIALS AND METHODS

### *Study site*

Banfora is a city of 35,000 inhabitants located in the southwestern part of Burkina Faso. Malaria is hyperendemic, with seasonal transmission strongly influenced by rainfall. At the time of the study, there were a Maternal and Child Health (MCH) center and a maternity ward associated with the province hospital in Banfora. Strong support was given to the MCH center by the provincial health department (education of pregnant women, vaccination campaigns, etc.) and the staff was highly motivated. As a result, approximately 80% of the pregnant women living in the city attended the prenatal center at least once before delivery. As noted above, che-

moprophylaxis with chloroquine was not recommended by the Ministry of Health, and a preliminary study established that self-administered chemoprophylaxis was rare among pregnant women.

*Study design*

Between February 1987 and February 1988, every pregnant woman attending the MCH center was included in the study. At the first visit (before the fifth month of pregnancy for the majority of the women), information on ethnicity and parity was recorded. Two local investigators and a supervisor were hired and trained in Bobo-Dioulasso, Burkina Faso, then relocated to Banfora, where they were in charge of the followup. They explained the principles of the trial to the women, and those willing to participate gave their verbal consent and were included in the study. For the sake of simplicity, an alternate allocation of treatment was performed, in which the women were divided into two groups (treated and control). Women in the treated group were given 300 mg of chloroquine sulfate (Nivaquine Forte; Specia Laboratories; Rhone-Poulene Sante, Paris, France) once a week, as recommended by the WHO. For technical reasons, it was not possible to give a placebo to women in the control group. On each visit (once a week at the patient's home) until delivery, information about the health of the woman and the intake of drugs since the last visit was collected. A blood film and a fingerprick sample for serologic studies were collected every two weeks. The oral intake of chloroquine by women in the treated group was supervised by the investigator at the time of the domiciliary visit.

At the time of delivery, information on the newborn baby (particularly clinical status and birth weight) and anthropometric indices of the mother (weight, size, triceps skinfold, etc.) were recorded. Samples from maternal and cord blood and from placenta were collected for serologic analysis and examined for malaria parasites. Samples were identified with a number, stained, refrigerated as needed, and sent twice a week to the ORSTOM laboratory in Bobo-Dioulasso, where slide examination and serologic assays were carried out. Thick and thin blood films and placental smears were stained with Giemsa. At least 200 fields were examined for malaria parasites before a slide was considered negative. More than 95% of the identified parasites were *Plasmodium falciparum.* Laboratory technicians had no information on the status of the individuals from whom the samples had been taken, as did the midwives who weighed the newborn babies. One of the two principal investigators (M. C. or A. R.) visited the study area at least twice a week.

To ensure both the quality of data collection and adherence to the study design, additional investigations were performed three times on 20 randomly chosen women. Questionnaire data were checked and urine samples were tested for the presence of amino quinolines using the Haskins test.[14, 15] During the main investigation, resistance to chloroquine was spreading in West Africa. After the study was terminated, an investigation on in vivo sensitivity to chloroquine of *P. falciparum* isolated from a sequential sample of pregnant women attending the MCH center was carried out.[16]

*Statistical analysis*

Differences in proportions were tested using Pearson's chi-square test. The Armitage test was used to evaluate trends in relative risk (RR) estimates.[17] The RR confidence limits were calculated according to the formula of Greenland and Robins.[18] Differences between means were tested using the Student's *t*-test.

## RESULTS

*Description of the populations*

One thousand five hundred forty women were enrolled in the study (Figure 1). Seventy-six of these were studied separately; 24 had started a prophylaxis by themselves before the first visit to the MCH center (volunteer group), and 52 refused to participate (refusal group). The remaining 1, 464 women were divided into two groups: 745 treated (weekly prophylaxis) and 719 controls (no prophylaxis). At the beginning of the investigation, one of the investigators incorrectly classified women willing to take a prophylaxis (but not having initiated it) in the volunteer group instead of in the treated group. These women were reassigned to the treated group a few days later; this explains the disproportion in numbers observed between the treated and control groups.

There were slightly more exclusions from the

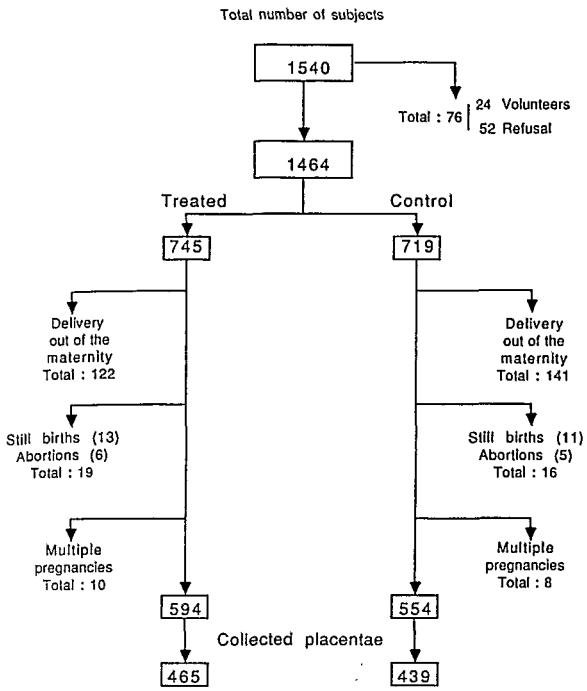


FIGURE 1. Composition of the subject and control populations in the randomized trial of chloroquine prophylaxis during pregnancy in Banfora, Burkina Faso (1987–1988).

control group than from the treated group between the beginning of the study and the time of delivery. Most of these exclusions represented women who delivered outside the hospital (141 in the control group and 122 in the treated group); the larger number of exclusions in the control group may be due to better motivation in the women receiving prophylaxis. Other reasons for exclusion (abortions, still births, multiple pregnancies) were equally distributed between the two groups (29 and 24, respectively). Overall, 594 in the treated group and 554 in the control group could be followed until the end of their pregnancy and gave birth to a live child.

*Characteristics of treated and control subjects*

As shown in Table 1, the treated and control groups were comparable for age, parity, district of habitation, ethnic group, duration of followup, and nutritional status (mean value of weight-for-height index or Quetelet's index = 22.0 for the treated group and 22.2 for the control group, not significant).

*Compliance with treatment*

Fifteen women from the treated group received no prophylaxis. They were either lost to

TABLE 1

*Characteristics of the treated and control groups in this study*

| Characteristic | Treated | | Controls | |
|---|---|---|---|---|
| | No. | (%) | No. | (%) |
| Age (years) | | | | |
| <20 | 126 | (17.1) | 114 | (16.1) |
| 20–24 | 216 | (29.4) | 220 | (30.9) |
| 25–30 | 191 | (26.0) | 185 | (26.0) |
| 30–35 | 119 | (16.2) | 107 | (15.0) |
| >35 | 83 | (11.3) | 85 | (12.0) |
| Gestation rank | | | | |
| 1 | 106 | (14.4) | 113 | (15.9) |
| 2–3 | 239 | (32.6) | 212 | (29.8) |
| 4–5 | 178 | (24.3) | 182 | (25.6) |
| >5 | 211 | (28.7) | 204 | (28.7) |
| District | | | | |
| Central | 384 | (52.3) | 381 | (53.6) |
| Peripheral | 350 | (47.7) | 328 | (46.4) |
| Ethnic group | | | | |
| Bobo | 35 | (4.9) | 47 | (6.9) |
| Dioula | 78 | (11.0) | 80 | (11.7) |
| Dagari | 32 | (4.5) | 34 | (5.0) |
| Mossi | 130 | (18.4) | 132 | (19.3) |
| Peul | 44 | (6.2) | 46 | (6.7) |
| Senoufo | 307 | (43.4) | 288 | (40.7) |
| Samo | 37 | (5.2) | 35 | (5.1) |
| Other | 45 | (6.4) | 22 | (3.2) |
| Duration of followup (months) | | | | |
| <2 | 145 | (21.6) | 125 | (19.8) |
| 2–3 | 143 | (21.3) | 132 | (20.9) |
| 3–4 | 151 | (22.5) | 130 | (20.6) |
| 4–5 | 108 | (16.1) | 139 | (22) |
| >5 | 125 | (18.6) | 106 | (16.8) |

followup or delivered within a week after the first visit to the MCH center. Sixty-four women from the control group were treated with antimalarial drugs during their pregnancies. At the first examination, two women had a strongly positive Haskins test result associated with the administration of chloroquine by one of the local investigators. Subsequent examinations detected no additional incorrect classifications by the investigators.[15] The remaining 62 women independently took a short treatment since they believed they had malaria.

*Additional investigation*

Evaluation of the in vivo sensitivity of *P. falciparum* to chloroquine showed that none of the 36 women tested carried a resistant strain, indicating a therapy success rate of > 99%.[16]

TABLE 2

*Proportion of infected placentae by duration of prophylaxis*

| Duration of treatment (weeks) | Infected placenta | Uninfected placenta | Relative risk* |
|---|---|---|---|
| Control | 83 | 354 | 1.0 |
| Treated (weeks) | | | |
| <4 | 5 | 41 | 0.57 (0.24–1.34) |
| 4–7 | 4 | 57 | 0.35 (0.13–0.91) |
| 8–11 | 4 | 118 | 0.17 (0.06–0.46) |
| >12 | 6 | 228 | 0.14 (0.06–0.30) |
| Total treated | 19 | 444 | 0.22 (0.13–0.35) |

* Values in parentheses are 95% confidence intervals. Armitage test for trend to duration of prophylaxis: $\chi^2_T = 62.52$; 1 degree of freedom; $P < 10^{-6}$.

*Effect of prophylaxis on placental infection*

Nine hundred four placentas were collected and examined from the 1, 148 women in whom followup was possible. Data on chemoprophylaxis were incomplete for four women, who have not been included in the analysis. The relative risk of placental infection in the treated group decreased with increasing duration of prophylaxis (Table 2) when compared with those in the control group. The RR of placental infection was 0.57 when the duration of prophylaxis was less than one month, and it decreased significantly (0.35, 0.17, and 0.14 over one-month periods) when the duration of prophylaxis increased. There was a significant linear trend of decreased infection with the duration of prophylaxis (Armitage test for trend $\chi^2_T = 62.52$; 1 degree of freedom [df]; $P < 10^{-6}$).

Thus, it can be concluded that prophylaxis is not effective when administered for less than one month. Fourteen women who received chloroquine for more than one month had a placental infection. Six of them had taken it irregularly or had stopped the treatment at least two weeks before delivery. The eight remaining women had been taking their treatment correctly, but the placentas showed low parasite densities (usually <100 parasites/ml of blood).

*Comparison of birth weights in the treated and control groups*

This comparison was performed in the 1, 148 women who were followed until the end of their pregnancies (Figure 1). The average difference between birth weights in the two groups was 5.6 g ($P$ not significant) (Table 3). The relative risk of having a low birth weight (< 2, 500 g) for a newborn child was not decreased by prophylaxis (RR = 0.99, 95% confidence intervals [CI] = 0.76–1.29, $\chi^2 = 0.003$; df = 1, not significant) (Table 4).

Since the primigravidae appear to be a high-risk group for low birth weight (LBW), birth weight comparisons were also performed in the treated (n = 106) and untreated (n = 113) nulliparae. The average difference in birth weight was 82 g ($P = 0.25$; not significant) and the relative risk of having an LBW was 0.88 (95% CI = 0.64–1.21, $\chi^2 = 0.64$; df = 1, not significant).

*Relationship between placental infection and birth weight*

Placentas were collected from 904 of the 1, 148 followed women (Figure 1). Mean birth weights were higher among children whose mothers had uninfected placentas (difference of 113 g; $P < 0.02$) (Table 5), and the relative risk of having an LBW for a newborn baby was increased by placental infection (RR = 1.76, 95% CI = 1.22–2.54, $\chi^2 = 8.59$; df = 1; $P < 0.005$) (Table 6).

## DISCUSSION

The randomized trial performed in Banfora confirmed the association between placental infection and LBW. The administration of chloroquine during pregnancy proved to be highly protective against infection of the placenta with malaria parasites. However, the difference in mean birth weight between the treated and con-

TABLE 3

*Relationship of mean birth weight (in grams) to inclusion status (treated or control)*

| | Treated | Control | Difference* |
|---|---|---|---|
| Mean value | 2,937.8 | 2,932.2 | 5.6 (−46.8–58) |
| Standard error of the mean | 452.5 | 467.4 | |
| Number of subjects | 594 | 554 | |

* Values in parentheses are 95% confidence intervals.
$t$-test value = 0.2; 1, 146 degrees of freedom; not significant.

TABLE 4

*Proportion of low birth weights (less than 2,500 g) by inclusion status (treated or control)*

| | Treated | | Control | | |
|---|---|---|---|---|---|
| | No. | (%) | No. | (%) | Relative risk* |
| Birth weight, <2,500 g | 97 | (16.3) | 91 | (16.4) | 0.99 (0.76–1.29) |
| Birth weight, >2,500 g | 498 | | 463 | | |

* Values in parentheses are 95% confidence intervals.
$\chi^2 = 0.003$; 1 degree of freedom; not significant.

trol groups was very small and not statistically significant.

These results may be explained in two ways. First, the prevalence of placental malaria was relatively low (19%) among the untreated women. With a mean 113-g deficit in birth weight attributable to placental malaria, the overall expected effect of prophylaxis in the treated group would be 113 × 0.19 or 21.5 g/pregnancy. In the sample we studied, the observed difference between the two groups should have been greater than 50 g to be statistically significant. Such a difference would have led to the conclusion of a direct effect of malaria on birth weight, but would this difference be sufficient to justify a generalized mass prophylaxis? Since primigravidae are known to be a high-risk group for both malaria and LBW,[2–5, 8] we compared birth weights in this subset of women. The difference between the treatment groups was higher than in the overall population (82 g), but was not statistically significant. Such an absence of a difference can be attributed to the small sample size, and we would expect a higher effectiveness of the prophylaxis when given only to primigravidae, as suggested in a recent study in Gambia.[19]

Second, malaria is associated with other factors (nutritional status, ethnic origin, duration of pregnancy, etc.) that are known to cause LBW, and its relative importance may not be as high as generally believed. The 6 g difference in birth weight observed between the treated and control groups is lower than the expected difference of 21.5 g, which suggests that malaria is not the only relevant factor. An ongoing multivariate analysis will attempt to evaluate the role of malaria when other risk factors are taken into account.

Two potential sources of bias could be identified in this study. First, some women were erroneously classified in the volunteer group at the beginning of the trial. They should have been excluded from the study, and not reclassified in the treated group a few days later. Unfortunately, these subjects were not clearly identified, and it was impossible to exclude them afterwards. Since their number was relatively small (approximately 20 subjects), and a comparison of the treated and control subjects showed no difference between the two groups, this misclassification is unlikely to have been a major source of bias. Second, the loss of contact with subjects during the followup was more prevalent in the control group than in the treated one (141 versus 122). This difference was due mainly to women who delivered at home. We performed another comparison between the two groups at the end of the followup, which showed no statistical differences for age, parity, district of habitation, ethnic group, and nutritional status. It is, therefore, unlikely that bias resulting from the loss of followup had any appreciable effect on our results.

To our knowledge, two studies have been performed on the effect of antimalarial prophylaxis on the course and outcome of pregnancy. In 1972, McGregor and Avery[10] demonstrated in the Solomon islands an important increase in birth weight associated with a decrease in malarial

TABLE 5

*Relationship of mean birth weight (in grams) to placental infection*

| | Infected placenta | Uninfected placenta | Difference* |
|---|---|---|---|
| Mean value | 2,842.2 | 2,955.2 | 113 (9.54–216.45) |
| Standard error of the mean | 513.2 | 450.4 | |
| Number of subjects | 104 | 800 | |

* Values in parentheses are 95% confidence intervals.
*t*-test value = 2.37; 902 degrees of freedom; $P < 0.02$.

TABLE 6
*Proportion of low birth weights (less than 2,500 g) by placenta infection*

| | Infected placenta | | Uninfected placenta | | |
|---|---|---|---|---|---|
| | No. | (%) | No. | (%) | Relative risk* |
| Birth weight, <2,500 g | 27 | (26.0) | 118 | (14.8) | 1.76 (1.22–2.54) |
| Birth weight, >2,500 g | 77 | | 682 | | |

* Values in parentheses are 95% confidence intervals.
$\chi^2 = 8.59$; 1 degree of freedom; $P < 0.005$.

prevalence after an insecticide spraying campaign. Placental infection rates were not recorded, but the prevalence of malarial infection in the 2–9-year-old age group before spraying was 29.7%, and decreased to 12.8% after spraying. The increase in mean birth weight was 165 g, and there was a corresponding decrease in the LBW rate from 20.5% to 11.8%. This study was discussed by Kramer[12] who estimated that given a placental infection rate of 40% and a 170-g deficit among women with placental malaria, the attributable impact of malaria would be 170 × 0.40 = 68 g/pregnancy, which is much lower than the 165-g decrease estimated by McGregor and Avery. This indicates that other factors may have played a role in the difference observed in this study. Since the two groups in this study were not strictly comparable (the study design was a comparison of the same population with a two-year interval, and not a randomized trial), the conclusions made by the investigators should be viewed with caution. In our randomized trial, the observed placental infection rate was 19%, and as mentioned above, the expected attributable impact of malaria on birth weight was moderate (21.5 g), which seems a more reasonable estimate with respect to the analysis of Kramer. More recently, Greenwood and others studied the efficacy of a pyrimethamine prophylaxis given by traditional birth attendants in Gambia.[19] Placental prevalences were not recorded, but the investigators reported a marked effect of prophylaxis on birth weight in primigravidae; there was no significant effect on the overall population.

In conclusion, since the causal impact of malaria on birth weight is uncertain, the prevalence of placental malaria is low in many areas, the compliance to a generalized prophylaxis program is generally poor,[20] and there is a rapid spreading of chloroquine-resistant *P. falciparum* throughout Africa, the effect of an extension of chloroquine prophylaxis to all pregnant women might be disappointing in terms of birth weight improvement. However, a policy of giving chemoprophylaxis only to primigravidae might be recommendable, provided that the administration of antimalarial drugs during a first pregnancy does not increase susceptibility to malaria during the second pregnancy.[9, 19] This question is being investigated in Cameroon, where we are following the second pregnancies of women protected with chloroquine during their first pregnancy.

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