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INCREASE OF BIRTH WEIGHT FOLLOWING CHLOROQUINE CHEMOPROPHYLAXIS DURING THE FIRST PREGNANCY: RESULTS OF A RANDOMIZED TRIAL IN CAMEROON

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Abstract. A randomized trial was carried out from 1991 to 1993 among women attending an antenatal clinic in Ebolowa, Cameroon where malaria is hyperendemic and transmission occurs at a high level all year round. All pregnant women attending the clinic for their first prenatal visit between October 1991 and November 1992 were alternately assigned to chloroquine (CQ) or control (CT) groups. Chloroquine was given under observation at a weekly oral dose of 300 mg. At delivery, smears from maternal, cord, and placental blood were made and stained with Giemsa for parasites. An in vivo chloroquine sensitivity investigation was carried out on women attending the postnatal consultation to evaluate the level of chloroquine resistance in the target population. The efficacy of chloroquine was moderate in placental infection (39.2% infected in the CQ group versus 57.8% in the CT group: $P = 0.05$), probably because of a resistance to chloroquine estimated to be 10.9%. In the CQ group, the mean birth weight was significantly higher ($P = 0.02$) and the proportion of low birth weight newborns was lower (10.5% versus 27.7%; $P = 0.02$). A strong correlation between placental infection and birth weight was observed: the mean birth weight difference between infected and noninfected placentae was 359 g ($P < 0.0001$) and the proportion of low birth weight new born babies was 35.6% versus 5.9% ($P = 0.0001$). In Cameroon, in spite of a moderate resistance to chloroquine, this drug proved to be highly effective in increasing birth weight when administered to primigravidae. We therefore think such a prophylaxis should be recommended only to primigravidae in high transmission areas.

In areas of high endemicity, malaria during pregnancy can induce such harmful effects as maternal anemia and low birth weight in newborns.[1–4] Although the World Health Organization has responded by recommending malaria chemoprophylaxis during pregnancy,[5] recent studies show that application to all women irrespective of their parity could have disappointing results.[6,7] One alternative might be to restrict chemoprophylaxis solely to primigravidae, the group most vulnerable to malaria[8,9] and the delivery of low birth weight babies (Kortmann HF, 1972, *Malaria and Pregnancy.* M.D. Thesis, Drukkerij Elinkwijk, Utrecht, The Netherlands).[2,10] However, the increase of *Plasmodium falciparum* resistance to chloroquine could reduce the efficacy of this inexpensive and well-tolerated drug. Other drugs such as dapsone-pyrimethamine[7] or mefloquine[4] may be considered for use, but they are expensive and have greater side effects.

Prophylaxis with either chloroquine or amodiaquine is generally recommended in Cameroonian antenatal clinics; however, compliance among pregnant women is poor. To investigate the effects of regular chloroquine administration on primigravidae in an area where there is moderate resistance to the drug, we conducted a controlled chemoprophylaxis trial in a semirural region of Cameroon.

SUBJECTS AND METHODS

Subjects. The study lasted from October 1991 to April 1993 and was carried out on pregnant women attending the antenatal clinic at Enongal Hospital in Ebolowa, Cameroon. The town of Ebolowa, with a population of 35,000, is situated 160 km south of Yaounde. Pregnant women taking part in the study had to be living either in the town or within a 25-km radius of its center. This peripheral zone consists of small villages set in the midst of traditionally farmed cocoa plantations, the region's prime source of income. While the Boulou are the main ethnic group, the town is inhabited by a large colony of Bamileke, whose members originate from the western part of the country and are usually involved in business and commerce. The region is dominated by tropical rain forests and malaria here is hyperendemic, with a high rate of transmission occurring all year round.

After being examined by the hospital physician, any primigravida living in the study area and attending the clinic for a first prenatal visit between October 1991 and November 1992 was introduced to an investigator who obtained their informed consent and allocated them alternately to a chloroquine treatment (CQ) group or a control (CT) group. Each woman's age, ethnicity, residence, and socioeconomic status (Table 1) was recorded.

Women belonging to the CQ group received one 300-mg oral dose of chloroquine (Nivaquine Forte®; Rhone Poulenc Sante Laboratory, Antony, France) per week under observation from the first visit until delivery. Women in the CT group, on the other hand, followed the usual hospital procedures; placebos were not used 1) in case anyone eventually contracting malaria rejected proper treatment in the false belief that they were already being treated, and 2) because of technical difficulties of reproducing the exact amount of the chloroquine tablets.

Once a week, each of the women was visited at home by an investigator, asked about febrile episodes and drug intake between visits, and had her axillary temperature taken. Thick blood smears were made once every two weeks in the absence of febrile episodes, or at the time of the visit when a temperature exceeded 38°C. If a CQ group woman showed

TABLE 1
Characteristics of treated and control subjects on entry into the study

Characteristics	Treated		Controls	
	No.	(%)	No.	(%)
Age (years)				
≤15	13	(9.9)	14	(10.4)
15.1–17	38	(29)	45	(33.3)
17.1–19	41	(31.3)	40	(29.6)
19.1–21	23	(17.6)	20	(14.8)
21.1–23	7	(5.3)	12	(8.9)
>23	9	(6.9)	4	(3)
Socioeconomic status*				
Low	11	(11)	22	(19.3)
Medium	50	(50)	57	(50)
High	39	(39)	35	(30.7)
District				
Central	98	(74.8)	96	(71.1)
Peripheral	33	(25.2)	39	(28.9)
Ethnic group				
Boulou	69	(52.7)	82	(60.7)
Bamileke	27	(20.6)	21	(15.6)
Mbam	10	(7.6)	10	(7.4)
Other	25	(19)	22	(16.3)

* Study subjects interviewed by investigators were given scores according to the following criteria: dwellings: floors, concrete (1 point) or mud (0 points); walls, concrete (1) or mud (0); roofs, corrugated iron (1) or thatched (0); domestic equipment: (1 point if positive): refrigerator, radio, television, automobile, motorbike. According to their scores, the socioeconomic status was then categorized as low (1–2 points), medium (3–5 points), or high (6–8 points).

signs of having had a suspected attack of malaria, defined as an association of hyperthermia and parasitemia, or as an isolated parasitemia of more than 5,000 parasites per microliter of blood, this was taken to mean that chloroquine treatment was failing, and such cases were treated with oral quinine. Women in the CT group showing similar signs were administered a therapeutic dose of chloroquine (25 mg/kg of body weight) and, if this had no effect, oral quinine (10 mg/kg, three times a day for seven days).

The protocol was examined and officially approved by the Comite National d'Ethique (Paris, France) and the Comite d'Ethique (Ministere de la Sante du Cameroun).

Investigators recorded outcomes of pregnancies and detailed information on newborns (clinical status and birth weight) at the time of delivery at the Enongal Hospital maternity ward. Maternal, cord, and placental blood samples were also taken and examined for parasites.

Approximately halfway through the study, positive cases of *P. falciparum* infection among all postnatal clinic outpatients who had delivered at Enongal were identified by means of fingerprick blood smears. They were then treated with chloroquine and underwent in vivo testing to investigate parasite sensitivity to the drug. The parasitemia was checked seven days later according to an adult application of the protocol described by Breman and others.[11]

Laboratory methods. Thick blood smears were stained with Giemsa and 100 oil-immersion microscopic fields were examined for malaria parasites. Parasites and white blood cells were enumerated, and parasite density was calculated according to an assumed average of 8,000 leukocytes/mm^3.

Statistical methods. Data were analyzed with BMDP statistical software (BMDP Statistical Software, Inc., Los Angeles, CA). The chi-square test was used to test differences in proportions and analysis of variance was used to test differences in means. Relative risk (RR) confidence limits were calculated according to the formula of Greenland and Robins.[12] Multiple linear regression and logistic regression were used to test the effect of chloroquine intake and other covariates on birth weight.

RESULTS

Study population. Two hundred sixty-six women were enrolled in the study. One hundred thirty-one of them in the CQ group had weekly prophylaxis administered by the investigators, while the other 135 (CT group) women, knowing that they would be treated with chloroquine or quinine at the first sign of infection, consented to receiving no therapy. The CQ and CT groups were compared on the basis of age, ethnicity, residence, and socioeconomic status. Table 1 shows that on entering the study, no difference between the two groups was recorded for any of these variables.

For personal reasons entirely unrelated to the trial, three women withdrew from the CQ group and four left the CT group shortly after enrollment, and we lost contact with 14 CQ and 10 CT group subjects during follow-up. Eleven women from the CQ group and 15 from the CT group had just settled in Ebolowa; they had normal follow-up at the beginning before returning to their home provinces a few weeks prior to delivery.

One hundred three women from the CQ group and 106 from the CT group remained in the study area and were followed for the duration of their pregnancies. Twenty-three and 17, respectively, delivered in their home villages, so our investigators were unable to measure the birth weight of their newborns. The same was true of the 16 CQ-treated and 19 control subjects who went into the maternity wards of the Province Hospital. One CQ-treated subject delivered before the first investigator visit and was thus not administered any chloroquine. Having consequently had neither prophylaxis nor follow-up, this woman was excluded from the final analysis. In the end, we were reduced to analyzing the 63 CQ group and 70 CT group women who lasted the course and whose babies were eventually delivered and weighed at Enongal Hospital.

No differences were found with regard to residence, duration of follow-up, and socioeconomic status when the two groups were compared at delivery (Table 2), although the CT group women appeared to be younger ($\chi^2 = 13.37$; degrees of freedom [df] = 5; $P = 0.02$) and proportionally more of them were ethnic Boulous than Bamilekes ($\chi^2 = 11.44$; $df = 4$; $P = 0.02$).

Compliance with chemoprophylaxis and resistance to chloroquine. By the time of delivery, the 63 CQ women had been administered an average total of 2,500 mg of chloroquine (i.e., 8.3 weekly intakes during follow-up).

Of the CT group women, 39 (56%) declared that on their own initiative, they had taken one or more short (generally infratherapeutic) treatments of either chloroquine or amodiaquine during the course of their pregnancy because they thought they had contracted malaria. The investigators treated an additional 19 CT group women for suspected malaria attacks with chloroquine (25 mg/kg over a three-day period) and then, in the case of treament failure, oral quinine (10

TABLE 2
Characteristics of treated and control subjects at delivery

Characteristics	Treated No.	Treated (%)	Controls No.	Controls (%)
Age (years)				
≤15	2	(3.2)	8	(11.4)
15.1–17	15	(23.8)	26	(37.1)
17.1–19	19	(30.2)	13	(18.6)
19.1–21	15	(23.8)	10	(14.3)
21.1–23	5	(7.9)	11	(15.7)
>23	7	(11.1)	2	(2.9)
Socioeconomic status*				
Low	4	(7.5)	10	(16.6)
Medium	24	(45.3)	31	(51.7)
High	25	(47.2)	19	(31.7)
District				
Central	47	(74.6)	47	(67.1)
Peripheral	16	(25.4)	23	(32.9)
Ethnic group				
Boulou	28	(44.4)	50	(71.4)
Bamileke	18	(28.6)	7	(10.0)
Mbam	7	(11.1)	5	(7.1)
Other	10	(15.8)	8	(11.4)
Duration of follow-up (months)				
≤2	13	(20.6)	17	(24.3)
2.1–3	8	(12.7)	15	(21.4)
3.1–4	15	(23.8)	17	(24.3)
4.1–5	10	(15.9)	13	(18.6)
>5	17	(27.0)	8	(11.4)

* For additional information, see Table 1.

mg/kg, three times a day for seven days). Four women were found to be vomiting and were thus admitted to the hospital for parenteral quinine treatment. Of the CQ group women, seven showed signs of malaria attacks and were treated with above-mentioned dose of oral quinine. Five were admitted to the hospital for parenteral treatment.

The in vivo chloroquine sensitivity investigation showed that 10.9% (95% confidence interval [CI] = 1.9–19.9%) of the 46 parasitemic women attending postnatal clinic consultations still had positive smears seven days after chloroquine treatment (25 mg/kg of body weight).

Effect of prophylaxis on placental infection. One hundred twenty placental smears were collected and examined. Thirty-seven (57.8%) from 64 CT group women were found positive, as were 22 (39.3%) from 56 CQ subjects ($\chi^2 = 4.1$; df = 1; $P = 0.043$; Table 3), showing a 32% protective efficacy of regular chloroquine prophylaxis.

Effect of prophylaxis on birth weight. There were two spontaneous abortions in the CT group, four babies were stillborn (two in each group), and five were delivered by Caesarean section (two in the CT group and three in the CQ group) and their weights were not recorded. The mean birth weight of the 122 remaining babies in the two groups was compared. It was significantly higher in the CQ group than in the CT group (a difference of 207 g; $P = 0.02$; Table 4). The relative risk of low birth weight (< 2,500 g) in a newborn was also significantly reduced by prophylaxis (RR = 0.38, 95% CI = 0.16–0.89, $\chi^2 = 5.66$, $P = 0.02$; Table 5). There was no birth weight more than 4,000 g in the CQ group and only one (4,550 g) in the CT group.

Age and ethnicity distribution in the two Enongal groups changed between enrollment and delivery (Table 2). Age was higher in the CQ group, and this variable (but not ethnicity) was correlated with placental infection, with older women having fewer placental infections $\chi^2 = 16.62$; df = 5; $P = 0.03$). We performed multiple regression to assess the relationship between chloroquine intake and birth weight, taking all covariates into account. Neither age nor other covariates significantly influenced birth weight; after adjustment for all variables, the difference between the two groups was 230.2 g (Table 6). Logistic regression on low birth weight showed similar results (Table 7) (odds ratio for having a low birth weight given that the mother belongs to the CQ group = 0.20, 95% CI = 0.05–0.78, no effect of other covariates)

Relationship between placental infection and birth weight. Mean birth weights were much higher when placentas were not infected (difference of 358 g; $P < 10^{-4}$; Table 8), and placental infection increased the relative risk of a newborn with a low birth weight (RR = 7.24, 95% CI = 2.28–22.98, $\chi^2 = 17.64$. df = 1; $P < 10^{-4}$; Table 9).

TABLE 3
Proportion of infected placentae by inclusion status

	Treated No.	Treated (%)	Controls No.	Controls (%)	RR*
Infected placenta	22	(39.3)	37	(57.8)	0.68 (0.46–0.99)
Uninfected placenta	34	(60.7)	27	(42.2)	

* RR = relative risk. Numbers in parentheses indicate 95% confidence limits. $\chi^2 = 4.10$, degrees of freedom = 1, $P = 0.043$.

TABLE 4
Mean birth weight (in grams) in relation to treatment status

	Treated	Controls	Difference*
Mean value	3,069.8	2,862.3	207.5
SEM†	56.8	68.0	(33.8–381.6)
Number of subjects	57	65	

* Numbers in parentheses indicate 95% confidence limits. *t*-test value = 2.3, degrees of freedom = 121, $P = 0.02$.
† SEM = standard error of the mean.

DISCUSSION

An earlier study conducted in Burkina Faso, an area of high endemicity with marked seasonal variations, showed that despite being very effective in preventing placental infection, administering chloroquine prophylaxis to all pregnant women in general had little effect on the mean birth

TABLE 5
Proportion of low birth weights (less than 2,500 g) by treatment status

	Treated No.	Treated (%)	Controls No.	Controls (%)	RR*
Birth weight <2,500 g	6	(10.5)	18	(27.7)	0.38 (0.16–0.89)
Birth weight ≥2,500 g†	51	(89.5)	47	(72.3)	

* RR = relative risk. Numbers in parentheses indicate 95% confidence limits. $\chi^2 = 5.66$, degrees of freedom = 1, $P = 0.017$.
† Only one birth weight was greater than 4,000 g in the control group (none in the treated group).

TABLE 6

Multiple linear regression on birth weight, accounting for treatment status, socioeconomic status, duration of follow-up, district, and age

Variable	Coefficient	F*
Constant	2,590.7	
Inclusion status	230.2	5.10
Socioeconomic status	−30.5	0.97 (NS)
Duration of follow-up	1.2	0.95 (NS)
District	3.4	0.94 (NS)
Age	13.3	0.56 (NS)

* NS = not significant.

weight of their babies.[6] Analysis of the primigravidae subset showed a higher, although not statistically significant, difference in birth weights between the treated and control groups than was the case in the population as a whole. One explanation for these results was that as far as birth weight was concerned, chloroquine had no noticeable effect among multigravidae, while primigravidae, a known high-risk group for malaria and low birth weight, were the only ones benefiting from prophylaxis. Similarly to our findings in Burkina Faso, literature on the subject shows that three other chemoprophylaxis trials[7, 13, 14] were unable to prove an overall effect on birth weight, yet noted a trend towards an increase, albeit not statistically significant, in birth weights among the offspring of primigravidae. In one of these studies,[7] Greenwood and others demonstrated a significant difference in the subset of primigravidae taking prophylaxis for more than six weeks. Only one trial has provided evidence of a probable overall increase in birth weights between treated and control groups among all pregnant women in general.[15]

Since placental malaria prevalence was moderate in Burkina Faso (19% in the control group), we decided to conduct another study in a region where transmission was higher to accurately evaluate the efficacy of chloroquine prophylaxis when restricted to primigravidae.

Our results in Cameroon establish that regular, supervised chloroquine administration is effective in primigravidae and, for the first time among this subset of females, a highly significant 207-g difference in mean birth weights was observed between the treated and control groups. The proportion of babies with low and very low birth weights was greatly reduced, and there was no obvious increase in high birth weight newborns. Garner and others[16, 17] feared that interventions leading to an increase in mean birth weight could paradoxically result in higher perinatal mortality due to a higher risk of obstructed labor. Our data and the recent work of Greenwood and others[18] does not confirm this hypothesis.

When we began the study, we decided to follow-up 250 women during their pregnancy to end up with 200 subjects (100 in each group) at delivery. This was thought to be a sufficiently sized sample for detecting the least possible effect of prophylaxis on birth weight. Unfortunately, however, follow-up contact was lost with an unexpectedly high number of women between enrollment and delivery and the trial time limits did not allow for replacements. The most likely reason for so many losses was the severe economic crisis that hit Cameroon during that period. The majority of the population in Ebolowa is economically dependent on the cocoa trade. As raw material prices continued to decrease, women were unable to afford to deliver at Enongal Hospital and preferred either to stay home or to go to the Province Hospital where lower fees were charged. There were no other obvious reasons for not giving birth at Enongal because the hospital's reputation remained at a consistently high level throughout the period of the study. In the end, the CQ and CT groups both lost an almost equal number of subjects (67 and 65, respectively).

The intervention groups changed in composition between enrollment and the end of the study. At the beginning, both groups were similar for all variables; at delivery, however, there were more Bamileke and fewer Boulou in the CQ group and, on average, women were older than in the CT group. Neither of these two variables (age and ethnicity) was related to birth weight and age was the only one that could be linked to placental infection. We performed a regression analysis and a logistic regression eliminating the influence of all other variables and confirming that the only relevant factor for an increase in birth weight was prophylaxis intake.

We had previously used chloroquine in Burkina Faso where at the time of the trial, there was, if anything, a negligible rate of resistance to the drug. In Ebolowa, our find-

TABLE 7

Logistic regression on low birth weight, accounting for treatment status, duration of follow-up, ethnicity, district, age, and socioeconomic status*

Variable	Exponential (coefficient) (OR)	OR 95% CI	P†
Inclusion status	0.20	(0.05–0.78)	0.01
Duration of follow-up	–	–	0.57 (NS)
Ethnicity	–	–	0.71 (NS)
District	–	–	0.72 (NS)
Age	–	–	0.75 (NS)
Socioeconomic status	–	–	0.79 (NS)
Constant	–	–	$<10^{-4}$

* OR = odds ratio; CI = confidence interval. Values of the OR are not given since this variable is not binary-coded and cannot be calculated from the exponential values of the coefficient.
† NS = not significant.

TABLE 8

Mean birth weight (in grams) in relation to placental infection

	Infected placenta	Uninfected placenta	Difference*
Mean value	2,766.6	3,125.2	358.6
SEM†	65.6	55.6	(190–527.1)
Number of subjects	59	61	

* Numbers in parentheses indicate 95% confidence limits. t-test value = 4.18, degrees of freedom = 119, $P < 0.0001$.

TABLE 9

Proportion of low birth weights (less than 2,500 g) by placental infection

	Infected placenta		Uninfected placenta		
	No.	(%)	No.	(%)	RR*
Birth weight <2,500 g	21	(35.6)	3	(4.9)	7.24 (2.28–22.98)
Birth weight ≥2,500 g	38	(64.4)	58	(95.1)	

* RR = relative risk. Numbers in parentheses indicate 95% confidence limits. $\chi^2 = 17.64$, degrees of freedom = 1, $P < 0.0001$.

ings showed a 10% resistance to chloroquine, and one might have thought that a more effective drug could have been chosen. As stressed by Nahlen and others,[19] "the strategy for diminishing the impact of malaria in pregnancy needs effective and safe drugs for treatment and chemoprophylaxis, an efficient system for delivering the drugs, and acceptance of drugs by pregnant women". Only a few drugs are actually safe for use during pregnancy. Although pyrimethamine may be a long-used and well-accepted treatment, apart from rarely reported accidents such as agranulocytosis or a teratogenic effect observed on rats but never proven in humans,[7] the degree of resistance to this drug makes it less effective than chloroquine in areas where transmission is high.[19] Proguanil alone or in association with chloroquine is safe but must taken daily, which raises questions about the compliance of such a regimen in public health policies. Mefloquine has not yet been established as safe[4, 17] and its price is still too high to be offered to African women in systematic chemoprophylaxis.

Thus, chloroquine remains one of the best prophylactic drugs for areas of hyperendemicity. It is inexpensive, well-accepted, and well-tolerated (especially in its 300-mg coated form that allows for a single weekly administration). It has proved to be highly effective in increasing birth weight in the newborns of primigravidae. While restricting it to this group of women can improve the feasibility of health policies aimed at preventing malaria during pregnancy, the most serious problem remains actually getting them to comply without supervision.[20, 21]

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REFERENCES

1. McGregor IA, Wilson ME, Billewicz WZ, 1983. Malaria infection of the placenta in Gambia, West Africa: its incidence and relation to stillbirth, birthweight and placental weight. *Trans R Soc Trop Med Hyg 77:* 232–244.
2. Jelliffe EFP, 1968. Low birthweight and malarial infection of the placenta. *Bull World Health Organ 38:* 69–78.
3. Brabin BJ, 1983. An analysis of malaria in pregnancy in Africa. *Bull World Health Organ 61:* 1005–1016.
4. Steketee RW, 1989. Recent findings in perinatal malaria. *Bull Int Paediatr Assoc 10:* 418–433.
5. World Health Organization, 1984. Advances in malaria chemotherapy. Report of a WHO Scientific Group. *World Health Organ Tech Rep Ser 711.*
6. Cot M, Roisin A, Barro D, Yada A, Carnevale P, Breart G, 1992. Effect on birth weight of chloroquine chemoprophylaxis during pregnancy: results of a randomized trial. *Am J Trop Med Hyg 46:* 21–27.
7. Greenwood BM, Greenwood AM, Snow RW, Byass P, Bennett S, Hatib N'jie AB, 1989. The effects of malaria chemoprophylaxis given by traditional birth attendants on the course and outcome of pregnancy. *Trans R Soc Trop Med Hyg 83:* 589–594.
8. McGregor IA, 1984. Epidemiology, malaria and pregnancy. *Am J Trop Med Hyg 33:* 517–525.
9. Steketee RW, Breman JG, Paluku KM, Moore M, Roy J, Ma-Disu M, 1988. Malaria infection in pregnant women in Zaire: the effects and the potential for intervention. *Ann Trop Med Parasitol 82:* 113–120.
10. Spitz AJW, 1959. Malaria infection of the placenta and its influence on the incidence of prematurity in eastern Nigeria. *Bull World Health Organ 21:* 242–244.
11. Breman JG, Gayibor A, Roberts JM, Sexton JD, Agbo K, Miller KD, Karsa T, Murphy K, 1987. Single-dose chloroquine therapy for *Plasmodium falciparum* in children in Togo, West Africa. *Am J Trop Med Hyg 36:* 469–473.
12. Greenland S, Robins JM, 1985. Estimation for a common effect parameter from sparse follow-up data. *Biometrics 41:* 55–68.
13. Hamilton PJS, Gebbie DAM, Wilks NE, Lothe F, 1972. The role of malaria, folic acid deficiency and haemoglobin AS in pregnancy at Mulago hospital. *Trans R Soc Trop Med Hyg 66:* 594–602.
14. Fleming AF, Ghatoura GBS, Harrison KA, Briggs ND, Dunn DT, 1986. The prevention of anaemia in pregnancy in primigravidae in the Guinea savanna of Nigeria. *Ann Trop Med Parasitol 80:* 211–233.
15. Morley D, Woodland M, Cuthbertson WFJ, 1964. Controlled trial of pyrimethamine in pregnant women in an African village. *Br Med J i:* 667–668.
16. Garner P, Kramer MS, Chalmers I, 1992. Might efforts to increase birthweight in undernourished women do more harm than good? *Lancet 340:* 1021–1023.
17. Garner P, Brabin B, 1994. A review of randomized controlled trials of routine antimalarial drug prophylaxis during pregnancy in endemic malarious areas. *Bull World Health Organ 72:* 89–99.
18. Greenwood AM, Menendez C, Todd J, Greenwood BM, 1994. The distribution of birth weights in Gambian women who received malaria chemoprophylaxis during their first pregnancy and in control women. *Trans R Soc Trop Med Hyg 88:* 311–312.
19. Nahlen BL, Akintude A, Alakija T, Nguyen-Dinh P, Ogunbode O, Edungbola LD, Adetoro O, Breman JG, 1989. Lack of efficacy of pyrimethamine prophylaxis in pregnant Nigerian women. *Lancet ii:* 830–834.
20. Kaseje DCO, Sempebwa EKN, Spencer HC, 1987. Malaria chemoprophylaxis to pregnant women provided by community health workers in Saradidi, Kenya. I. Reasons for non-acceptance. *Ann Trop Med Parasitol 81 (suppl 1):* 77–82.
21. Brabin BJ, Ginny M, Alpers M, Brabin L, Eggelte T, Van Der Kaay, 1990. Failure of chloroquine prophylaxis for falciparum malaria in pregnant women in Madang, Papua New Guinea. *Ann Trop Med Parasitol 84:* 1–9.