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Effect of chloroquine prophylaxis during pregnancy on maternal haematocrit

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Two controlled trials of chloroquine prophylaxis during pregnancy were performed, one in Burkina Faso in 1987, on all pregnant women, and the other in Cameroon in 1992, on primigravidae only. Maternal haematocrit at delivery was found to be significantly higher in those women who had received chloroquine than in those who had not, both in Burkina Faso (37.4% *v.* 36.5%; $P = 0.01$) and in Cameroon (34.8% *v.* 32.8%; $P = 0.02$). Anaemia, defined as an haematocrit of $< 30\%$, was also less common in those treated with chloroquine (6.3% *v.* 8.5% in Burkina Faso and 8.3% *v.* 18.4% in Cameroon) but this difference was not significant in either country. A slight improvement in haematological status when prophylaxis is given has also been observed in similar studies performed in other tropical countries. The present results confirm the usefulness of targeting antimalarial prophylaxis at pregnant women. Such prophylaxis during the first pregnancy also increases birthweight.

In endemic areas, the main consequence of malaria during pregnancy is a reduction in birthweight, especially among first-born children (Jelliffe, 1968; McGregor *et al.*, 1983; Brabin, 1983; Meuris *et al.*, 1993; Morgan, 1994; Menendez, 1995). In women in general and in primigravidae in particular, parasitaemia during the first half of pregnancy may be associated with anaemia (Kortmann, 1972; Reinhardt *et al.*, 1978; Fleming *et al.*, 1986; Brabin *et al.*, 1990, Shulman *et al.*, 1996), contributing to maternal morbidity. According to Brabin *et al.* (1990), maternal anaemia may also have a direct effect on placental function, causing low birthweight (LBW).

Trials in two African cities, by Cot *et al.* (1992, 1995), explored the efficacy of weekly prophylaxis with chloroquine in preventing placental infections with *Plasmodium falciparum* and in reducing the proportion of LBW babies. The impact of the prophylaxis on maternal haematocrits at the time of delivery in the same trials was assessed in the present study.

SUBJECTS AND METHODS

The trials were conducted in two African cities of comparable size (i.e. about 35 000 inhabitants each): Banfora in Burkina Faso, in 1987; and Ebolowa in Cameroon, in 1992. Malaria is hyperendemic in both cities. Although transmission is seasonal and strongly influenced by rainfall in Burkina Faso, it is perennial in Cameroon.

All pregnant women (Burkina Faso) or all primigravidae (Cameroon) attending the local mother-and-child-health (MCH) centre for their first prenatal visit during a 1-year period

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were randomized to receive chloroquine (Nivaquine Forte; Rhone Poulenc) prophylaxis (300 mg each week until delivery) or no antimalarial prophylaxis. All were visited weekly at home and the outcomes of their pregnancies and detailed information on their babies were recorded at the time of delivery. Each woman's age, ethnicity, residence (both trials), socio-economic status (Cameroon) and parity (Burkina Faso) were recorded on enrolment (see Cot *et al.*, 1992, 1995). Protocols were officially approved by the Comité National d'Ethique (Paris, France) and by local ethical committees in Africa.

At delivery, samples of peripheral blood from the mother, cord blood and placental blood were taken, stained with Giemsa and examined for parasites. Peripheral-blood haematocrits were measured immediately after sampling, using a microhaematocrit centrifuge. Women were considered to be anaemic if their haematocrit was $<30\%$.

In each country, an investigation on in-vivo parasite sensitivity to chloroquine was performed on outpatients attending postnatal clinics who were found to be parasitaemic. Each was given a total of 25 mg/kg spread over 3 days and checked for parasitaemia 7 days later.

Data were analysed with BMDP statistical software (BMDP, Los Angeles, CA). Proportions were compared using χ^2 tests and mean haematocrits were compared by analysis of variance. Relative-risk confidence limits were calculated according to the formula given by Greenland and Robins (1985).

RESULTS

Subjects

Although 1540 pregnant women in Burkina Faso and 266 primigravidae in Cameroon were enrolled, only 1148 and 133, respectively, were successfully followed weekly from their first visit at the MCH centre until delivery. Only data from those who were seen on every scheduled home visit were analysed. In each country, the chloroquine (CQ) and control (CT) groups were comparable for all recorded variables on admission and, in spite of the unexpectedly high number of defaulters in Cameroon (mainly because of the costs), there were no major differences between the two groups at delivery (see Cot *et al.*, 1992, 1995).

Effect of Prophylaxis on Placental Infection

By the time of delivery, each of the 594 subjects left in the CQ group in Burkina Faso had been given a mean total dose of 3 500 mg (representing 11.7 weekly intakes) and the 63 remaining in the CQ group in Cameroon had received a mean of 2 500 mg (8.3 weekly intakes).

Placentas were examined from 904 women in Burkina Faso and 120 in Cameroon (see Table 1). CQ prophylaxis reduced the prevalence of placental infection in Burkina Faso [4.1% v. 19%; $\chi^2 = 49.6$; one degree of freedom (df); $P < 0.0001$] and in Cameroon (39.3% *v.* 57.8%; $\chi^2 = 4.1$; df = 1; $P = 0.043$).

In the tests on local parasite sensitivity to CQ, none of the 36 parasitaemic women who received the drug in Burkina Faso was found positive 7 days after treatment (indicating a sensitivity of $>99\%$) whereas five (10.9%) of the 46 treated in Cameroon remained positive and possibly carried resistant strains of *P. falciparum*.

Effect of Prophylaxis on Haematocrit

Mean haematocrit values were recorded at delivery for 975 subjects in Burkina Faso and 97 in Cameroon (Table 1). For all subjects in each country, haematocrits in the CQ group were significantly higher than those in the CT group ($P = 0.01$ in Burkina Faso and $P = 0.02$ in Cameroon). The mean haematocrit for all CQ subjects (Cameroon and Burkina Faso combined) was also significantly higher than that for all CT subjects (37.2% *v.* 36.2%; $P = 0.002$). However, the difference in mean haematocrits between CQ primigravidae and CT primigravidae in Burkina Faso was not significant.

In each country, the frequency of anaemia (i.e. haematocrit $<30\%$) was less in the CQ group than in the CT (Table 1) but the difference was not statistically significant.

TABLE 1

Effects of chloroquine (CQ) prophylaxis on the prevalence of placental infection and anaemia and maternal haematocrit at delivery

Variable and study area	*Subjects*	*CQ group**	*Control group**	*Relative risk and (95% CI)*	*Difference in means and (95% CI)*
PLACENTAL INFECTION (% of subjects)					
Burkina Faso	All women	4.1 (463)	19 (437)	0.22 (0.13–0.35)	–
	Primigravidae	5.9 (68)	34.9 (63)	0.17 (0.06–0.46)	–
Cameroon	Primigravidae	39.3 (56)	57.8 (64)	0.68 (0.46–0.99)	–
HAEMATOCRIT (%)					
Burkina Faso	All women	37.4 (505)	36.5 (470)	–	+ 0.9 (0.2–1.6)
	Primigravidae	38.2 (70)	36.7 (75)	–	+ 1.5 (− 0.3–3.3)
Cameroon	Primigravidae	34.8 (48)	32.8 (49)	–	+ 2.0 (0.4–3.6)
Total	All parities	37.2 (553)	36.2 (519)	–	+ 1.0 (0.3–1.7)
PREVALENCE OF ANAEMIA (%)†					
Burkina Faso	All women	6.3 (505)	8.5 (470)	0.85 (0.65–1.11)	–
	Primigravidae	7.1 (70)	9.3 (75)	0.85 (0.43–1.70)	–
Cameroon	Primigravidae	8.3 (48)	18.4 (49)	0.59 (0.25–1.36)	–
Total	All parities	6.9 (553)	9.4 (519)	0.69 (0.46–1.04)	–

* Values in parenthesis are numbers of subjects.
† Anaemia defined as an haematocrit of $< 30\%$.
CI, Confidence interval.

TABLE 2
Relationship between malaria and maternal anaemia

Variable and study area	*Placenta**		*Difference in means and (95% CI)*	*Relative risk and (95% CI)*
	Infected	*Uninfected*		
MEAN HAEMATOCRIT (%)				
Burkina Faso	37.4 (671)	35.6 (85)	+ 1.8 (0.56–3.04)	–
Cameroon	34.9 (46)	32.7 (61)	+ 2.2 (0.47–3.90)	–
PREVALENCE OF ANAEMIA (%)†				
Burkina Faso	14.1 (85)	6.6 (671)	–	2.15 (1.18–3.91)
Cameroon	15.7 (51)	10.9 (46)	–	1.44 (0.51–4.10)

* Values in parenthesis are numbers of subjects.
† Anaemia defined as an haematocrit of < 30%.
CI, Confidence interval.

Severe anaemia (i.e. haematocrit < 13%; Fullerton and Turner, 1962) was only detected in one subject, in the CT group in Burkina Faso.

Relationship Between Malaria and Haematocrit (Table 2)

Placental malarial infection was strongly associated with low haematocrit in both Burkina Faso ($P = 0.005$) and Cameroon ($P = 0.01$) and with high frequency of anaemia in Burkina Faso ($P = 0.01$) but not in Cameroon ($P = 0.49$). In Burkina Faso, there was no apparent association between gravidity and haematocrit ($P = 0.31$) or frequency of anaemia ($P = 0.66$).

DISCUSSION

Various factors may be involved in the aetiology of anaemia during pregnancy in developing countries, including iron and folate deficiencies and haemoglobinopathies (Fleming *et al.*, 1986; Fleming, 1989). However, the major cause seems to be malaria, as shown by the commonly observed association between maternal or placental infection and low haemoglobin or haematocrit (Gilles *et al.*, 1969; Hamilton *et al.*, 1972; Nosten *et al.*, 1991; Matteelli *et al.*, 1994; Shulman *et al.*, 1996; present study). The present results from Burkina Faso, unlike those of Jackson *et al.* (1991) and Shulman *et al.* (1996), failed to show higher malaria prevalence among primigravidae than among other pregnant women.

There have been several trials on the use of antimalarial drugs in pregnant women from endemic areas, most of which were reviewed by Garner and Brabin (1994). Unfortunately, few such trials have met satisfactory standards for randomization (Table 3) and the methods of detecting anaemia and the thresholds used to define it vary between the trials. However, the results of most of these studies have shown that there were small increases in haemoglobin concentration or haematocrit in the groups receiving antimalarial prophylaxis (Hamilton *et al.*, 1972; Kortmann, 1972; Fleming *et al.*, 1986; Spencer *et al.*, 1987; Greenwood *et al.*, 1989; Nosten *et al.*, 1994). The present study involved trials in two areas which differ greatly in terms of malaria transmission. In Cameroon, where transmission is perennial, haematocrits were generally lower than in Burkina Faso, where transmission is seasonal, even if primigravidae from each country are compared. The prevalence of anaemia in the present, untreated subjects (14% in Burkina Faso and 16% in Cameroon) was lower than reported in several earlier investigations; most (72%–80%) of the women investigated in Zaire by Jackson *et al.* (1991), Kenya by Shulman *et al.* (1996) and

TABLE 3

Effect of malaria prophylaxis on haematocrit (Ht, %) or haemoglobin concentration (Hb, g/dl) in pregnant women, as detected in earlier studies

		Treated			*Untreated*				
Subjects	*Drug*	N	*Ht*	*Hb*	N	*Ht*	*Hb*	*Difference in means and (95% CI)*	*Reference*
All parities	Chloroquine	751	37.0	–	1095	36.6	–	+0.36 (0.01–0.71)	Hamilton *et al.* (1972)
All parities	Chloroquine	24	–	11.4	35	–	10.1	+1.3 (ND)	Kortmann (1972)
All parities	Chloroquine	127	–	9.95	111	–	9.62	+0.33 (ND)	Spencer *et al.* (1987)
Multigravidae	Dapsone–pyrimethamine	126	30.7	–	118	30.4	–	+0.3 (−0.7–1.3)	Greenwood *et al.* (1989)
Primigravidae	Dapsone–pyrimethamine	21	30.1	–	11	26.6	–	+3.5 (0.7–6.3)	Greenwood *et al.* (1989)
Multigravidae	Mefloquine	128	31.5	–	125	32.3	–	−0.8 (−1.7–0.1)	Nosten *et al.* (1994)
Primigravidae	Mefloquine	43	34.4	–	43	32.0	–	+2.4 (1.0–3.8)	Nosten *et al.* (1994)

CI, Confidence interval; ND, not determined.

Tanzania by Matteelli *et al.* (1994) were found to be anaemic. Similarly the prevalence of severe anaemia in the present study (one case among 1072 subjects or $<0.1\%$) was much lower than the 9.3% seen in Tanzania (Matteelli *et al.*, 1994) and the 9.8% seen among Kenyan primigravidae (Shulman *et al.*, 1996). The present subjects may be healthier than those investigated in earlier studies because of their relatively good nutritional status and better access to malaria treatment. When asked, 64 of the 554 Burkinabe CT women and 39 of the 70 Cameroonian CT women said that they had taken a short course of antimalarial treatment (on their own initiative and usually at infratherapeutic doses) during the course of their pregnancies. Even with this complication, the trial in each country showed that maternal haematocrit was slightly but significantly improved by the administration of CQ throughout pregnancy.

Although the full effect of anaemia on maternal morbidity and mortality remains to be investigated, it is likely that severe anaemia contributes to maternal deaths in tropical countries (Fullerton and Turner, 1962). Maternal morbidity is difficult to assess, but LBW in neonates has been associated with maternal anaemia at delivery (Reinhardt *et al.*, 1978; Harrison *et al.*, 1985; Fleming, 1989, Brabin *et al.*, 1990). Furthermore, in a 2-year follow-up of women participating in a trial of mefloquine prophylaxis in Thailand, Nosten *et al.* (1994) showed that mortality was higher among children whose mothers were anaemic at their delivery. Similarly, in Papua New Guinea, Brabin *et al.* (1990) reported an increased rate of perinatal mortality in children born to women with severe anaemia at delivery.

Malaria therefore appears to be a major cause of anaemia during pregnancy, which in turn contributes significantly to mother and child morbidity and mortality. The improvements seen in birthweights and the albeit moderate improvements in the haematological status of pregnant women in endemic areas when given antimalarials must justify routine use of malaria prophylaxis in this group.

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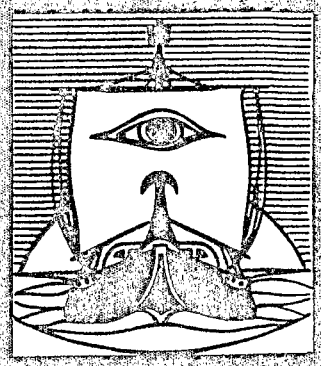

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