A review of randomized controlled trials of routine antimalarial drug prophylaxis during pregnancy in endemic malarious areas

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Current global recommendations for routine malaria chemoprophylaxis in pregnant women living in endemic malarious areas are not clear. To assist in policy formulation, the evidence from randomized controlled trials was reviewed. The literature was extensively searched, and studies identified were systematically analysed in relation to outcomes in the mother and the baby.

Routine chemoprophylaxis appears to have an effect on antenatal morbid episodes and packed cell volume. There is a trend towards higher birth-weight values in chemoprophylaxis groups, which reached statistical significance in some studies. Evidence of an effect on gestation was only examined in one study. The effects on perinatal and neonatal mortality have only been examined in a few studies, with small sample sizes.

The analysis questions whether routine malaria chemoprophylaxis is the best use of scarce resources in developing countries, and suggests that chemoprophylaxis might be targeted at anaemic women and primigravidae. Large controlled trials, with treatment available to placebo groups, are required to test whether routine chemoprophylaxis has advantages over early, effective treatment of clinical malaria.

Introduction

Although malaria in pregnancy has been extensively researched, debate concerning antimalarial chemoprophylaxis during pregnancy continues. First and second pregnancies are associated with a higher prevalence of *Plasmodium falciparum* parasitaemia in the first half of pregnancy in women living in endemic malarious areas (*1*). Malaria may contribute to antenatal anaemia (*2*), and slowing of fetal growth, especially in primigravidae (*3*). Clinical episodes in late pregnancy may cause preterm delivery in non-immune women, although in semi-immune women a few studies suggest that growth retardation occurs more frequently than preterm delivery (*3–5*). Elimination of malaria, for example, by residual spraying with insecticide, has been associated with an increase in mean birth weight (*6*). The presence of malaria parasites in the placenta is associated with low birth weight (*7, 8*); and maternal malaria infection, defined as the presence of parasites in the placenta or peripheral blood during labour, may be associated with a higher perinatal mortality (*9*).

In the past, WHO recommended routine malaria drug prophylaxis throughout pregnancy for women living in endemic malarious areas (*10*). Although routine chemoprophylaxis is still recommended, it is not always easy to ensure good compliance, even with targeted health promotion activities. Good compliance has been achieved in the context of special research studies (*11, 12*); other studies have demonstrated that good compliance may be difficult to achieve (*13*).

The potential efficacy of chemoprophylaxis with chloroquine is likely to be reduced with the emergence of chloroquine-resistant *Plasmodium falciparum*. Daily proguanil is an alternative, and good compliance has been reported in studies in Tanzania (Mutabingwa, personal, communication, 1992) and Nigeria (Fleming, personal communication, 1990). However, there is a question over whether a daily schedule would be widely acceptable in other settings. Pyrimethamine has few side-effects, but its use is limited by parasite drug resistance. The safety of other drugs, such as Maloprim (dapsone and pyrimethamine) or mefloquine, is less well established; and they are more expensive.

While the benefits of chemoprophylaxis in non-immune women are clear (*14*), the possible benefits in indigenous, semi-immune women are not so obvious. Currently, WHO recommends that "in settings

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where placental parasitaemia is associated with low birth weight, and an effective antimalaria drug can be provided on a regular basis, chemoprophylaxis may be considered" (*15*). The ambiguity of this statement reflects the current dilemma of policy-makers balancing efficacy of a potential chemoprophylactic agent against its potential adverse effects and the problems in delivering it. Some of the efficacy of chemoprophylaxis is based on an effect on birth weight: whether this necessarily affects perinatal or infant mortality has recently been questioned (*16*). Prevention of preterm delivery, on the other hand, could have an important impact on neonatal mortality.[a]

Before recommending chemoprophylaxis, with whichever drug regimen, to all pregnant women living in a particular endemic malarious area, clear evidence is required of its efficacy. To assist in this assessment, we have conducted a systematic review of the existing evidence derived from randomized controlled trials of chemoprophylaxis.

Materials and methods

Inclusion criteria. The criteria for inclusion in this review were trials during pregnancy in which an attempt had apparently been made to conduct a randomized comparison either between a policy of routine antimalarial chemoprophylaxis and a policy of treatment of symptomatic malaria; or between alternative antimalarial chemoprophylaxis regimens.

Trial identification. Trials were identified through existing literature reviews and a database of perinatal trials. Reference was made to Kramer (*3*), who reviewed the determinants of birth weight, searching the literature from 1970 to 1984; Brabin (*2*), who reviewed the risks and severity of malaria in pregnant women, and documented recent and current field studies; and the Oxford Database of Perinatal Trials, and the Cochrane Pregnancy and Childbirth Group, which maintains a register of published, unpublished, ongoing and planned trials concerned with perinatal health (*17*).

A MEDLINE search from 1966 to 1992 was conducted, searching titles and abstracts for "random", "malaria", and "pregnant or pregnancy". This process was repeated using EMBASE (1974 to 1992), a general medical database with a high coverage of European journals.

All the journals publishing relevant trials identified using the above methods were then systematically hand-searched for the period 1960–92, except those which had already been systematically searched for by staff compiling the Oxford Database of Perinatal Trials.

The final trials list was sent to the Special Programme for Research and Training in Tropical Diseases of the World Health Organization to check that all trials had been identified. In addition, citations to the selected trials were identified by the Science Citation Index database (SciSearch) from 1981 to 1992 as a final check. Methods and results from each study were systematically scrutinized. Any loss between the initial cohort of women and those included in the final analysis of outcomes was examined. Where information appeared to have been collected but was not fully reported, the authors were approached for further details where possible.

Description of trials. Nine published studies were identified (Table 1) (*11, 18–25*). Advance information from one further study was kindly provided by the investigators (*26*). Additional data from completed studies were kindly provided by Dr A. Greenwood (Gambia) and Dr T.K. Mutabingwa (Tanzania).

Setting. All but one of the studies were conducted in Africa (Table 1). Factors indicative of host immunity, including the level of endemicity (with respect to parasite prevalence and seasonal variation) were only sketchily reported on. Exposure risk as measured by the entomological inoculation rate was not given in any of the studies. Two of the studies were conducted in urban populations, where endemicity is likely to be low.

The studies occurred over some 30 years, during which time resistance of the parasite to a variety of antimalarial drugs developed. A qualitative description of suspected and confirmed parasite drug resistance in study areas was commented on in all papers published after 1988 (Table 1).

Characteristics of participants. All studies were of antenatal attenders. Thus the efficacy of chemoprophylaxis is only under test in this group by this delivery mechanism. In only one study (*11*) was the whole pregnant population examined, so that the outcome of pregnant women not attending clinics was available.

Methodological characteristics. Random allocation to experimental and control groups was described in six studies. Women were the unit of randomization in five studies, and compound inhabited in the sixth (Table 2). Two studies used alternate allocation; one used a quasi-random design dependent on which

[a] **Slutsker L et al.** *Neonatal mortality associated with low birthweight in Malawi.* 38th Annual Meeting of the American Society of Tropical Medicine and Hygiene, Hawaii, December 1989.

Table 1: **Studies identified between 1964 and 1993**

Study comparisons, first author, and year	Country and area	Malarial endemicity	*P. falciparum* drug resistance present?	Outcomes measured[a]				
				Antenatal (various)	Obstetric (type of delivery)	Birth weight	Gestation	Perinatal mortality
Chloroquine, pyrimethamine, proguanil, Maloprim or mefloquine compared with placebo/no antimalarial drug:								
Morley, 1964	Nigeria, Imesi	Holoendemic	None	+	–	+	–	+
Hamilton, 1972	Uganda, Kampala (urban)	<5% parasite prevalence at first visit	None	+	+	+	–	–
Martin, 1982	Cameroon, Yaounde	Unknown	None	+	–	+	–	–
Harrison, 1985	Nigeria, Zaria	Unstable endemicity with seasonal transmission	None	+	+	+	–	–
Fleming, 1986	Nigeria, Zaria	Unstable endemicity with seasonal transmission	None	+	+	+	–	+
Greenwood, 1989	Gambia, Farafenni	Seasonal transmission	None	+	–	+	–	+
Nahlen, 1989	Nigeria, Ilorin	Endemic	Possibly pyrimethamine	+	–	–	–	–
Cot, 1992	Burkina Faso, Banfora (urban)	Hyperendemic, with seasonal transmission	Probable chloroquine	+	–	+	–	–
Nosten, 1993	Thai-Burmese border refugee camp	Unstable, mesoendemic malaria	Multiple	+	+	+	+	+
Proguanil compared with chloroquine:								
Mutabingwa, 1991	Tanzania, Muheza	Hyper/holoendemic, with seasonal transmission	Chloroquine	+	+	+	–	+

[a] Measured is indicated by +; not measured by –.

clinic women were referred to. Loss or exclusions from the initial cohort that were entered into the trials varied from 60% to 3.5% (Table 2). Three studies appeared to be double-blind (*19, 21, 26*). In the study by Greenwood et al. (*11*), the study supervisors were aware of the status (whether control or placebo) and village dispensers may have deduced this from the different colour of placebo and active drugs. Only two studies (*11, 18*) reported on the duration of chemoprophylaxis; in particular, the proportion of women taking chemoprophylaxis for short periods was not usually noted, and this is an important factor when considering potential drug efficacy.

Comparison of interventions. Nine studies compared malaria chemoprophylaxis (either chloroquine, pyrimethamine, proguanil, Maloprim or mefloquine) with a placebo prophylactic drug or nothing. The other study compared a regimen of proguanil with chloroquine.

The dose of antimalarial drugs used in chemoprophylaxis may be insufficient to clear a current parasitaemia, and a therapeutic dose of antimalarial drugs at the start of chemoprophylaxis is often recommended. However, this regimen was only followed in three studies (Table 2). Only two papers describe access to treatment in the event of a malarial illness (*23, 26*), although it seems likely that in all the other studies subjects had access to treatment for illness.

Oral iron and folic acid supplements were used in some studies (Table 2). Various combinations were used in both antimalarial and comparison groups. Hamilton et al. (*20*) compared chloroquine prophylaxis plus ferrous sulfate with ferrous sulfate alone and ferrous sulfate plus folic acid. Two studies of primigravid Hausa women in Nigeria (*19, 21*) used similar study designs, comparing placebo with a single dose of chloroquine followed by proguanil prophylaxis. Each experimental group was divided into four subgroups: proguanil alone, proguanil plus iron, proguanil plus folic acid, and proguanil plus folic acid and iron.

Outcomes measured. The outcomes of each study were examined first with respect to the mother, which were classified as parasitaemia prevalence, prevalence of anaemia, incidence of morbidity, and mode of delivery. Second, the outcomes with respect to the baby were examined, which were placental infection, birth weight, gestation, and perinatal, neonatal or infant mortality.

Statistical methods. Weighted averages were calculated when necessary. In the two studies where standard deviations for birth weight were not provided (*22, 23*), an estimate of 500 g was used. Odds ratios with 95% confidence limits were calculated between antimalarial and control groups for each study for each outcome using standard methods for dichotomous and continuous data (*27*). Calculations were checked using meta-analysis software.

Results

Maternal effects

Parasitaemia. All studies that examined antenatal parasitaemia showed a significant effect of chemoprophylaxis in reducing the parasitaemia prevalence. This effect was observed even in multigravidae, where it was examined in two studies.

Haemoglobin/packed cell volume. Four studies examined haemoglobin or packed cell volume values during late pregnancy (Table 3). Two studies showed a positive effect with all parities combined. Greenwood et al. (*11*) showed a positive effect in primigravidae, but not multigravidae. One study, not included in the Table, examined haemoglobin values in primigravidae postnatally; no statistically significant difference in anaemia prevalence was found (*20*).

Morbidity. Only two studies examined clinical morbidity systematically. Morley et al. (*23*) found fewer complaints of fever in the experimental group, and Mutabingwa[b] found fewer clinical episodes of fever in both primigravidae and multigravidae.

Mode of delivery. Obstetric outcome was examined in four studies (Table 3). Interventions possibly indicating cephalopelvic disproportion (Caesarian section, forceps delivery, and craniotomy) were examined by treatment and control groups. In three studies, chemoprophylaxis was not statistically significantly related to the incidence of interventions. In the study by Harrison et al. (*21*), drug prophylaxis with proguanil was associated with a lower risk of obstetric intervention. However, some women in the proguanil group also received iron and/or folic acid, and in these women growth (height) also increased during pregnancy. The nutritional supplementation (not the chemoprophylaxis) appeared to assist maternal growth in pregnancy, and to reduce the risk of abdominal delivery. There was no difference in obstetric intervention between placebo alone (4/14) and proguanil alone (2/23), but the numbers were small.

[b] **Mutabingwa TK.** *Studies on malaria chemosuppression during pregnancy in Tanzania* (PhD thesis). Amsterdam, University of Amsterdam, 1993.

Table 2: **Subjects studied, and drug regimens used**

Study (first author)	Study population and entry criteria	Randomization process	Drug regimen in prophylaxis groups			Comparison group	Lost or excluded/ initial cohort	Final sample size	
			Prior therapeutic treatment	Antimalarial	Haematinics			Experimental	Control
Morley	Rural population, all antenatal attenders	Quasi-random (alternate assignment at registration)	No	Pyrimethamine monthly		Lactose tablets	72/292 (25)[a]	86	78
Hamilton	Antenatal clinic hospital attenders with complications, or at high risk of complications	Pseudo-random (based on referral to one of three clinics)	No	Chloroquine weekly	Ferrous sulfate	Ferrous sulfate alone, or with folate	689/1846 (37)	464	685
Martin	Antenatal clinic hospital attenders	Apparently randomly allocated, method not stated; not blind.	No	Chloroquine monthly or weekly	Nil	Nothing given	Not reported	40	37
Harrison	Hausa, under 16 years old, primigravidae, attending antenatal clinic	Randomly allocated, double-blind	Single dose chloroquine	Proguanil daily	None, or ferrous sulfate and/ or folate	Placebo	137/228 (60)	77	14
Fleming	Hausa primigravidae, less than 26 weeks gestation	Randomly allocated, double-blind; defaulters replaced	Single dose chloroquine	Proguanil daily	None, or ferrous sulfate and/ or folate	Placebo	18 replaced 36/200 (18)	111	32
Greenwood	All pregnant women in study area	Randomized by compound inhabited; not blind	No	Pyrimethamine & dapsone weekly	None	Placebo	None	518	531
Nahlen	Hospital and health centre antenatal attenders, <34 weeks gestation, no recent chloroquine	Random assignment	Yes	Pyrimethamine weekly	Folate and iron	Folate and iron	None	34	37
Cot	Urban population, all pregnant women attending antenatal clinics	Alternate allocation	No	Chloroquine weekly		Nil	392/1540 (25)	594	554
Nosten	Refugees; ≥20 weeks gestation, antenatal clinic attenders	Double-blind, random	Yes, if parasite positive	Mefloquine weekly	Folate and iron if anaemic	Placebo; folate and iron if anaemic	28/339 (8)	153	148
Mutabingwa	Antenatal attenders	Randomly assigned, not blind	Yes	Proguanil daily	Folate and iron	Chloroquine weekly	96/423 (23)	116	107

[a] Figures in parentheses are percentages.

Table 3: **Effect of prophylaxis on the mother**

Effect and study (first author)	Factor measured	Groups	Antimalarial prophylaxis group: occurrences/total, or mean (*n*)	Comparison group: occurrences/ total, or mean (*n*)	Odds ratio, or difference in the means (95% CI)
Maternal parasitaemia:					
Fleming	Parasite rates	28 weeks gestation	3/137	9/36	0.03 (0.01, 0.13)[a]
		36 weeks gestation	2/106	5/22	0.02 (0.00, 0.14)[a]
Greenwood	Parasite prevalence (last trimester)	Primigravidae	4/21	5/13	0.38 (0.08, 1.78)
		Multigravidae	9/120	21/103	0.33 (0.15, 0.72)[a]
Nahlen	Parasite prevalence after clearance	Primigravidae	6/23	6/22	0.94 (0.25, 3.48)
Mutabingwa	Parasite prevalence	Primigravidae	23/30	37/39	0.21 (0.05, 0.84)[a]
		Multigravidae	62/86	61/68	0.34 (0.15, 0.74)[a]
Nosten	Women infected at least once	All	5/153	37/148	0.16 (0.09, 0.32)[a]
Packed cell volume (PCV):					
Hamilton	PCV at last antenatal clinic visit	All	37.0 (751)	36.6 (1095)	+0.36 (0.01, 0.71)[a]
Martin	PCV at 40 weeks gestation	All	34.5 (40)	32.1 (37)	+2.4 (0.16, 4.64)[a]
Greenwood	PCV last trimester	Primigravidae	30.1 (21)	26.6 (11)	+3.5 (0.70, 6.3)[a]
		Multigravidae	30.7 (126)	30.4 (118)	+0.3 (–0.71, 1.31)
Nosten	PCV at term	Primigravidae	34.4 (43)	32.0 (43)	+2.4 (0.98, 3.82)[a]
		Multigravidae	31.5 (128)	32.3 (125)	–0.8 (–1.70, 0.1)
Antenatal morbidity:					
Morley	Fever incidence during pregnancy		21/119	45/108	0.31 (0.18, 0.56)[a]
Mutabingwa	Clinical malaria	Primigravidae	20/30	36/39	0.19 (0.06, 0.64)[a]
		Multigravidae	52/86	60/68	0.25 (0.12, 0.51)[a]
Obstetric outcomes:					
Hamilton	LSCS[b]	All parities (OK = 62%)[c]	60/404	70/614	1.36 (0.93, 1.98)
Harrison	LSCS for dysproportion, forceps, craniotomy	Primigravidae (OK = 40%)	8/77	5/14	0.13 (0.02, 0.65)[a]
Nosten	Complicated labour	All	9/153	9/148	0.97 (0.37, 2.5)

[a] Significant difference at the 5% level.
[b] LSCS = Caesarian section.
[c] OK = percentage of cohort where obstetric Outcome Known.

Greenwood et al. (*11*) was the only study to report on maternal mortality, with 1/518 deaths in the experimental and 3/531 deaths in the control group, and a further nine women died from the group not reporting for chemoprophylaxis. In all the other studies, pregnancy outcome data were largely dependent on hospital delivery for recording outcome. Considering the large number of women lost or excluded from the final analyses (Table 1), any results of maternal mortality are likely to be unreliable.

Fetal/neonatal effects

Placental parasitization. Two studies examined placental parasitaemia, and showed that chemoprophylaxis significantly reduced this. The study by Cot et al. (*18*) demonstrated an effect even in an area with presumed chloroquine resistance (Table 4).

Birth weight. Seven studies reported on mean birth weight values (Table 4). In the six studies that included multigravidae, five reported on the overall effect. Although four showed a trend towards higher mean birth weight, this was statistically significant in only one study. One study (*20*) reached a statistically significant difference when only regular attenders at the clinic were examined, thus only testing the intervention efficacy in a particular subgroup of women.

Five studies reported on birth weight in primigravidae (where an effect would be more readily

Table 4: **Effect of prophylaxis on the fetus**

Effect and study (first author)	Factor measured	Groups	Experimental group: occurrences/total, or mean ± SD (*n*)	Control group: occurrences/total, or mean ± SD (*n*)	Odds ratio, or difference in the means (95% CI)
Placental parasitaemia:					
Morley	Parasites present	All	1/115	18/105	0.13 (0.05, 0.33)[a]
Cot	Parasites present	All	19/444	83/437	0.24 (0.16, 0.36)[a]
Birth weight:					
Morley[b]	Birth weight	Primigravidae	2770 (27)	2579 (28)	+ 190 (–80, 460)
		Parity 1–3	2912 (93)	2844 (90)	+ 68 (–77, 214)
		Parity 4+	3060 (76)	2821 (78)	+ 248 (89, 407)[a]
		All parity groups	2954 (196)	2797 (196)	+ 157 (58, 256)[a]
Hamilton	Birth weight	Primigravidae	2935 ± 480 (114)	2895 ± 504 (167)	+ 40 (–77, 159)
		All	3020 ± 597 (464)	3008 ± 605 (685)	+ 23 (–62, 108)
		Regular attenders	3044 ± 520 (60)	2848 ± 660 (114)	+ 277 (43, 511)[a]
Martin[b]	Birth weight	All	3369 (40)	3137 (37)	+ 232 (–5.31, 460)
Fleming[c]	Birth weight	Primigravidae	2855	2723	+ 132 (NS)[d]
Greenwood	Birth weight	Primigravidae	2872 ± 330 (67)	2726 ± 465 (50)	+ 146 (–5.2, 297)[e]
		Parity 1–4	3101 ± 345 (173)	3074 ± 370 (194)	+ 31 (–46, 108)
		Parity 5+	3132 ± 350 (131)	3042 ± 380 (115)	+ 93 (1, 185)[a]
Cot	Birth weight	Primigravidae	NA (106)	NA (113)	+ 82 (NS)[d]
		All	2937 ± 452 (594)	2932 ± 467 (554)	+ 5.6 (–47, 58)
Nosten	Birth weight	All	2877 ± 433 (159)	2957 ± 496 (144)	– 80 (–182, 23)
Gestation:					
Nosten	Dubowitz assessment; less than 37 weeks	All	4/102	8/97	0.47 (0.15, 1.50)
Perinatal/neonatal mortality:					
Morley	Stillbirth/neonatal death	All	14/210	13/209	1.07 (0.49, 2.35)
Fleming[f]	Perinatal death	Primigravidae	11/128	5/32	0.45 (0.12, 1.66)
Greenwood	Stillbirth and perinatal death	Primigravidae	6/74	10/65	0.49 (0.17, 1.39)
		Multigravidae	22/427	27/446	0.84 (0.47, 1.50)
Nosten	Stillbirths	All	11/159	4/152	2.54 (0.90, 7.15)
Infant mortality:					
Nosten		All	25/144	24/144	1.05 (0.57, 1.94)

[a] Indicates a significant difference at the 5% level.
[b] Confidence limits estimated by us using birth weight standard deviation to be 500 g.
[c] Large number lost to follow-up for birth weight.
[d] NA = data not available; NS = difference tested by the researchers, and reported as not significant.
[e] Authors corrected for age and season, giving different values: +159 (95% CI: 8, 310).
[f] Incomplete follow-up.

demonstrated given their higher susceptibility to malaria). All showed a trend towards increased birth weight with chemoprophylaxis. Simple analysis of the data using 95% CI of the difference in the means did not show a significant effect in any of these studies. However, in the study by Greenwood et al. (*11*), an analysis by the authors adjusting birth weight for age and season demonstrated a significant difference between the experimental and control groups.

Stratification by parity in two studies failed to detect any effect on birth weight in women of mid-parity. In high parity women, the prophylaxis group had a significantly higher birth weight in both of the studies reporting on this subgroup.

Two studies examined the prevalence of low birth weight in primigravidae. In the study by Greenwood et al. (*11*), there were significantly fewer low-birth-weight infants in the experimental group (prophylaxis group, 4/67; control group, 11/50; OR=0.24 (95% CI: 0.08, 0.72)). In the study by Cot et al. (*18*) the difference was not statistically significant (OR=0.88 (95% CI: 0.64, 1.21)).

Only one study reports on the prevalence of high birth weight: this showed that two births greater than 4 kg in the prophylaxis group and none in the placebo group (2/144 (mefloquine), 0/143 (placebo) (*26*)). In the study by Greenwood et al. (*11*), the authors kindly provided unpublished data from the study showing that there was no statistically significant difference in the proportion of babies weighing more than 3.5 kg (Maloprim group, 60/430; placebo group, 50/145; OR=1.18 (95% CI: 0.79–1.77)) (A. Greenwood, personal communication, 1990). Thus the evidence for an effect on birth weight shows there is a tendency for a small positive effect in experimental groups. The lack of statistical significance may reflect a small effect overall, or an effect which only operates in certain subgroups of women.

Gestation. Only one study examined the duration of gestation, despite the fact that preterm delivery is highly predictive of neonatal mortality. The trend was towards fewer preterm infants in the treatment group, but the difference was not significant. The paucity of studies examining gestation probably reflects the difficulty in measuring gestation accurately (*16*).

Perinatal/neonatal mortality. Four studies systematically recorded stillbirth and perinatal, neonatal or infant mortality (Table 4). No study detected an effect on mortality. In two studies the trend was towards a protective effect in the chemoprophylaxis groups. The small size of all studies means that none had sufficient power to detect a possible effect.

Discussion

This review presents evidence that chloroquine, proguanil and mefloquine prophylaxis is associated with a reduction in antenatal illness episodes.

There is evidence from the controlled studies reviewed here and other work that chemoprophylaxis results in higher mean haemoglobin levels in pregnant women, that the higher prevalence of parasitaemia in the first half of pregnancy in primigravidae is associated with an increased risk of anaemia, and that moderate and severe anaemia in pregnant women is associated with poor maternal and fetal outcomes (*2*). While it is clear that starting chemoprophylaxis early in the first trimester of pregnancy in primigravidae is likely to be the most effective in preventing anaemia, precisely how early this needs to be for maximal efficacy is not known. In addition, the efficacy of chemoprophylaxis on anaemia in multigravidae has not been demonstrated, although anaemia remains prevalent in these women.

The presence of malaria parasites in the placenta is reduced by chemoprophylaxis, even when chloroquine is used in the presence of chloroquine-resistant malaria, as shown by Cot et al. (*18*). Although placental parasitization is associated with low mean birth weight in observational studies (*7*), it cannot be assumed that an intervention that reduces the prevalence of parasites in the placenta will automatically benefit the baby. An intervention that reduces the prevalence of maternal anaemia may be more beneficial.

This review shows a positive effect of chemoprophylaxis on mean birth weight in primigravidae and in grand multigravidae, but this is not a consistent finding. The effect of malaria on the human host varies in different parts of the world owing to differing biological, immunological and epidemiological circumstances affecting both the host and the parasite: this may account for the variation in the results obtained. When an effect on birth weight has been demonstrated, it is not clear if this is due to an effect on fetal growth or through an effect on the preterm delivery rate. Observational studies suggest that low birth weight in malarious areas is primarily associated with small infants or intrauterine growth retardation, not preterm delivery (*4, 5*). Preterm births have a higher mortality than term births of a similar weight (*28*), and evidence of a reduction in the preterm rate would be strong indirect evidence of a protective effect of chemoprophylaxis on mortality. In the absence of gestational age data, future studies should at the very least report on very low birth weight prevalence (less than 1500 g) as it is likely to be strongly associated with preterm birth in areas where the average birth weight tends to be low.

No study was of sufficient size to demonstrate a difference in perinatal mortality between experimental and control groups. While low birth weight is statistically associated with high perinatal mortality, and maternal malaria is associated with perinatal mortality (*9*), whether interventions that increase mean birth weight result in a concomitant reduction in mortality is open to question. Indeed, it can be hypothesized that increasing birth weight could result in higher, not lower, perinatal mortality (*16*). If infants born in malarious areas are normally proportioned, with head circumference and length values appropriate to their weight, it can be hypothesized that chemoprophylaxis may simply reduce the malarial effect and produce infants of a larger size, including a larger head. Although the overall effect on mean birth weight (where demonstrated) tends to be small, if the effect was occurring in a particular subgroup of women it is possible the effect could predispose those women to an increased risk of obstructed labour. Although in both the studies of Nosten and Greenwood there was a greater proportion of high birth weight babies in the chemoprophylaxis groups, the differences were not statistically

significant. To explore this further, we examined some observational data from McGregor et al. (*7*). The prevalence of high birth weight (≥4000 g) was 4.5% (231/5076) in those women with placentae negative for malaria parasites, compared with 2.7% (32/1183) in the positive group. This gives a relative risk of high birth weight with a parasite-negative placenta, compared with a positive placenta, of 1.7 (95% CI: 1.2, 2.4). However, in primigravidae, who may be at higher risk of cephalopelvic disproportion, no difference in prevalence of high birth weight infants between placental negative and positive groups was demonstrated. Although the data suggest that the absence of malarial infection in the placenta is associated with an increased prevalence of high birth weight infants, whether this is actually the result of the absence of malarial infection or some other confounding factor is not known.

Out of the four studies where obstetric outcome was examined, malarial prophylaxis was not associated with a worse obstetric outcome. Two studies were only of primigravidae, and one of these demonstrated a remarkable positive effect of iron or folic acid supplementation, but not malarial prophylaxis, on adolescent growth in pregnancy (*21*), and a reduction in the use of operative delivery in the women taking folic acid. However, the malarial prophylaxis was started relatively late in pregnancy (in the second trimester), after the peak of parasitaemia and occurrence of anaemia, so that haematinic drugs may be effective but antimalarial drugs not. On the other hand, the finding raises questions about the effects of malaria chemoprophylaxis in teenage mothers in the absence of iron or folic acid supplements, as birth weight may be increased but height and pelvic capacity may remain static, possibly resulting in a higher incidence of cephalopelvic disproportion. In women who have not received supplementation, and in whom the epiphyses have fused, malaria chemoprophylaxis leading to a larger baby may increase the risk of cephalopelvic disproportion. Although this remains as conjecture in the absence of data, it does emphasize the need to measure obstetric outcome in future clinical trials of prophylactic regimens. In the meantime, it highlights the need to maintain folic acid supplementation for all women receiving chemoprophylaxis.

Future work

There is a need for large, randomized controlled studies to examine malaria chemoprophylaxis interventions in relation to maternal health, perinatal and neonatal mortality, obstetric outcome, and the relationship with maternal growth. These studies should be placebo-controlled and double-blind, with careful attention to randomization, commencing early in pregnancy and preceded by a treatment of malaria infection. The endemicity of malaria in the study site needs describing in detail, in terms of both parasite prevalence and the morbidity it causes, as the effects of malaria on the human host vary considerably at different levels of endemicity and host immunity. Limiting the study to primigravidae only, in whom malaria infection is more prevalent, may be pragmatic for study design but will mean that questions about the effect in multigravidae remain unanswered.

The use of a placebo control group requires that all participants have ready access to antimalaria treatment when they develop symptoms. In theory, intermittent presumptive treatment (if correctly timed) may achieve equal efficacy to continuous chemoprophylaxis, so the study would demonstrate whether chemoprophylaxis had any additional advantage to simply treating malarious illness in pregnant women.

To answer questions about the effectiveness of routine prophylaxis in stable endemic areas, research needs to carried out in Africa because of its high level of cephalopelvic disproportion (*29*). Groups should receive iron and folic acid supplements. Outcomes to be measured must include maternal illness (malarial and non-malarial), obstetric outcome, infant gestation, and perinatal and neonatal mortality. The impact of routine prophylaxis in areas of epidemic, unstable malaria may be different: studies in parts of Asia, such as those being carried out by Nosten et al., will be important in answering questions concerning the effectiveness of routine prophylaxis in such areas.

At an international level, we need to clarify current WHO guidelines for women living in endemic malarious areas as regards (i) targeted chemoprophylaxis of anaemic women or primigravidae, and (ii) appropriate, early presumptive treatment of illness episodes in all pregnant women.

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Résumé

Essais contrôlés randomisés sur la prophylaxie antipaludique de routine pendant la grossesse dans les régions d'endémie palustre

Les recommandations mondiales actuelles en matière de chimioprophylaxie antipaludique de routine chez la femme enceinte dans les régions d'endémie palustre ne sont pas clairement définies. L'efficacité potentielle de la lutte antipaludique par chimioprophylaxie pendant la grossesse est limitée du fait de l'émergence de parasites résistants. L'innocuité des nouveaux médicaments est parfois moins bien établie que celle des médicaments classiques et ils peuvent être plus coûteux. De plus, l'administration de la chimioprophylaxie pendant la grossesse exige d'importantes ressources en matière de services de santé, et des efforts de promotion de la santé.

Nous avons examiné les données relatives aux essais contrôlés randomisés sur l'efficacité de la chimioprophylaxie antipaludique pendant la grossesse chez des femmes vivant dans des zones d'endémie. Toutes ces données ont été recherchées dans la littérature. Les études ont été systématiquement regroupées et analysées du point de vue des résultats de la prophylaxie chez la mère et l'enfant.

La chimioprophylaxie de routine semble avoir un effet sur les épisodes morbides anténatals et sur l'hématocrite. On observe une tendance à un poids de naissance plus élevé dans les groupes traités, de façon significative dans certains cas. Une seule étude a tenu compte de l'âge gestationnel. Les effets sur la mortalité périnatale et néonatale ont été peu étudiés sauf dans quelques études portant sur de faibles effectifs.

Cette analyse conduit à se demander si la chimioprophylaxie antipaludique de routine est le meilleur usage que l'on puisse faire de ressources limitées dans les pays en développement, et suggère que la chimioprophylaxie pourrait être axée sur les femmes anémiques et les primigestes. De vastes études contrôlées contre placebo offrant un traitement satisfaisant aux groupes placebo sont nécessaires pour établir si la chimioprophylaxie de routine présente des avantages sur le traitement précoce efficace du paludisme clinique.

References

1. **Brabin BJ.** An analysis of malaria in pregnancy in Africa. *Bulletin of the World Health Organization*, 1983, **61**: 1005–1016.
2. **Brabin B.** *The risks and severity of malaria in pregnant women.* Geneva, WHO (Applied Field Research in Malaria reports No. 1), 1991.
3. **Kramer MS.** Determinants of low birth weight: methodological assessment and meta-analysis. *Bulletin of the World Health Organization*, 1987, **65**: 663–737.
4. **Brabin BJ et al.** Consequences of maternal anaemia on outcome of pregnancy in a malaria endemic area in Papua New Guinea. *Annals of tropical medicine and parasitology*, 1990, **84**: 11–24.
5. **Garner PA et al.** Birthweight and gestation of village deliveries in Papua New Guinea. *Journal of tropical paediatrics* (in press).
6. **MacGregor JD, Avery JG.** Malaria transmission and fetal growth. *British medical journal*, 1974, **3**: 427–482.
7. **McGregor IA, Wilson ME, Billewicz WZ.** Malaria infection of the placenta in the Gambia, West Africa: its incidence and relation to stillbirth, birthweight and placental weight. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1983, **77**: 232–244.
8. **Steketee RW.** Recent findings in perinatal malaria. *Bulletin of the International Paediatric Association*, 1989, **10**: 418–433.
9. **Nyirjesy P et al.** Malaria during pregnancy: neonatal morbidity and mortality and the efficacy of chloroquine prophylaxis. *Clinical infectious diseases*, 1993, **16**: 127–132.
10. *Advances in malaria chemotherapy. Report of a WHO Scientific Group.* Geneva, World Health Organization, 1984 (WHO Technical Report Series, No. 711).
11. **Greenwood BM et al.** The effects of malaria chemoprophylaxis given by traditional birth attendants on the course and outcome of pregnancy. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1989, **83**: 589–594.
12. **Brabin BJ et al.** Failure of chloroquine prophylaxis for falciparum malaria in pregnant women in Madang, Papua New Guinea. *Annals of tropical medicine and parasitology*, 1990, **84**: 1–9.
13. **Kaseje DCO, Sempebwa EKN, Spencer HC.** Malaria chemoprophylaxis to pregnant women provided by community health workers in Saradidi, Kenya. I. Reasons for non-acceptance. *Annals of tropical medicine and parasitology*, 1987, **81**(S1): 77–82.
14. **Nathwani D et al.** Plasmodium falciparum malaria in pregnancy: a review. *British journal of obstetrics and gynaecology*, 1992, **99**: 118–121.
15. *Practical chemotherapy of malaria. Report of a WHO Scientific Group.* Geneva, World Health Organization, 1990, (WHO Technical Report Series, No. 805): 136.
16. **Garner P, Kramer MS, Chalmers I.** Might efforts to increase birthweight in undernourished women do more harm than good? *Lancet*, 1992, **340**: 1021–1023.
17. **Chalmers I et al.** The Oxford database of perinatal trials: developing a register of published reports of controlled trials. *Controlled clinical trials*, 1986, **7**: 306–324.
18. **Cot M et al.** Effect of chloroquine chemoprophylaxis during pregnancy on birthweight: results of a ran-

domized trial. *American journal of tropical medicine and hygiene*, 1992, **46**: 21–27.

19. **Fleming KA et al.** The prevention of anaemia in pregnancy in primigravidae in the guinea savanna of Nigeria. *Annals of tropical medicine and parasitology*, 1986, **80**: 211–233.
20. **Hamilton PJS et al.** The role of malaria, folic acid deficiency and haemaglobin AS in pregnancy at Mulago Hospital. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1972, **66**: 594–602.
21. **Harrison KA et al.** Growth during pregnancy in Nigerian teenage primigravidae. *British journal of obstetrics and gynaecology*, 1985, supp. **5**: 32–39.
22. **Martin GE, Nkwate CC.** Administration de la dose unique mensuelle de 600 mg de chloroquine base dans le contrôle du paludisme chez les femmes enceintes. *CEAC bulletin*, 1982, **53**: 41–47.
23. **Morley D, Woodland M, Cuthbertson WF.** Controlled trial of pyrimethamine in pregnant women in an African village. *British medical journal,* 1964, **1**: 667–668.
24. **Mutabingwa TK, Malle LN, Mtui SN.** Chloroquine therapy still useful in the management of malaria during pregnancy in Muheza, Tanzania. *Tropical and geographical medicine*, 1991, **43**: 131–135.
25. **Nahlen BL et al.** Lack of efficacy of pyrimethamine prophylaxis in pregnant Nigerian women. *Lancet*, 1982, **2**: 830–833.
26. **Nosten F et al.** Mefloquine prevents malaria during pregnancy: a double-blind placebo controlled trial. *Journal of infectious diseases* (in press).
27. **Bracken MB.** Statistical methods for analysis of effects of treatment in overviews of randomized trials. In: Sinclair JC, Bracken MB, Siverman WA, eds. *Effective care of the newborn infant*, Oxford, Oxford University Press, 1992: 13–18.
28. **Victora CG et al.** Birthweight and infant mortality: a longitudinal study of 5914 Brazilian children. *International journal of epidemiology*, 1987, **16**: 239–245.
29. **Harrison KA.** Mode of delivery with notes on rupture of the gravid uterus and vesicovaginal fistula. *British journal of obstetrics and gynaecology*, 1985, suppl. **5**: 61–71.