

# BRITISH MEDICAL JOURNAL

LONDON, SATURDAY 7 MAY 1983

## Malaria and pregnancy

The recent spate of reports<sup>1</sup> confirming the extension to parts of east Africa of chloroquine resistant strains of *Plasmodium falciparum*, which have been present for some time in other parts of the tropical world,<sup>2,3</sup> has caused much concern. Travel for business or pleasure has now become commonplace: in 1981 some 19 million Britons spent their holidays abroad, and many of them went to various exotic areas.<sup>4</sup> No wonder, then, that the news of changing trends in prevention of malaria by hitherto reliable drugs has caused some disquiet. In particular, many women want answers to three important questions. Does pregnancy aggravate malaria and vice versa? Can the available drugs always protect from malaria infection? Does the prevention of infection by antimalarial drugs have an adverse effect on the pregnancy or on the unborn child? Much has been written on these three topics and some aspects remain uncertain, but a consensus of expert opinion may be given.

Malaria in general, and especially an infection with *P falciparum*, is more hazardous during pregnancy. Pregnancy appears to interfere with the immune processes in malaria,<sup>5-7</sup> a disease which itself alters immune reactivity.<sup>8</sup> In highly endemic malarious areas, where semi-immune adults usually have substantial acquired resistance to local strains of plasmodia, the prevalence of clinical malaria is higher and its severity greater in pregnant women, especially during the second trimester, with the greatest risk in primiparas.<sup>5,7,9,10</sup>

The mechanism of this phenomenon is complex, with evidence of both suppression of antibody formation and depression of cell mediated immunity.<sup>8</sup> Malaria may cause abortion and premature labour; in tropical areas many pregnant women suffer from severe anaemia due to the infection itself and to the effects of deficiency of iron and folic acid.<sup>11,12</sup> The results of recent studies indicate that the anaemia of malaria is due to some extent to the immune destruction of sensitised red cells and a depression of erythropoiesis.<sup>13</sup>

Acute malaria in a pregnant woman requires speedy and complete treatment by the most effective drugs available, with full supporting medication.<sup>10,12,14,15</sup> Any fear that quinine at high therapeutic dosage may cause abortion is greatly exaggerated—and, moreover, severe malaria presents a far greater danger to the mother and the fetus. Congenital transmission of malaria may occur, though it is relatively rare; paradoxically, it is more frequent in babies born of non-immune mothers with malaria imported from tropical countries,

though massive infections of the placenta with *P falciparum* are common in immune mothers in highly endemic areas.<sup>5,9-12,14,16</sup>

Chemoprophylaxis of malaria throughout pregnancy, but particularly during its last third, is imperative for all non-immune women visiting endemic malarious areas. Prophylaxis is also advisable for all women permanently resident in tropical countries where malaria occurs.<sup>3,17-20</sup> The previously wide range of effective drugs available for chemoprophylaxis has now become restricted, because of the widespread resistance of *P falciparum* to antifolates (proguanil, pyrimethamine, trimethoprim) and the slow but steady extension of this resistance to 4-aminoquinolines (chloroquine, amodiaquine) and also to other drugs.<sup>18</sup> The use of a combination of pyrimethamine with sulfadoxine (Fansidar) or with dapsone (Maloprim) for preventing malaria in pregnant women is controversial, because of the alleged but unproved embryopathic action of pyrimethamine or possible effects of long-lasting sulphonamides on the blood forming organs of the fetus. For this reason Fansidar is not recommended for malaria prophylaxis in pregnancy by the World Health Organisation<sup>3</sup> or by its makers. Views are divided on the combination of pyrimethamine with dapsone (Maloprim). There is no evidence of any embryopathic effects when Maloprim is given at the recommended adult dose of one tablet a week. This dosage is adequate for fairly good protection from *P falciparum* malaria, even though the pharmacodynamics of the two active components are not well matched.<sup>2,17,18</sup> At higher dosage Maloprim may depress the bone marrow. In Britain expert opinion maintains that provided a woman takes folic or folinic acid (10 mg) daily she may take Maloprim during pregnancy; avoidance of the drug is not, we believe, justified by the evidence. Maloprim is not, however, recommended in France or the United States or by the World Health Organisation.<sup>3</sup> Furthermore, neither of the pyrimethamine-sulfadoxine or pyrimethamine-dapsone combinations are adequate for preventing malaria in areas with a high degree of resistance of *P falciparum* to pyrimethamine, or for full protection from infection with *P vivax*.

The conclusion seems to be that chloroquine and amodiaquine are still the best and comparatively the least harmful drugs for protecting pregnant women against *P vivax*, *P malariae*, *P ovale*, and chloroquine sensitive strains of *P falciparum*. Even in areas with some plasmodial resistance

to chloroquine fair protection will probably be obtained from a regular weekly dosage of 300 mg of chloroquine base during the stay in the endemic area and for at least four weeks after return to a temperate climate.<sup>18</sup> Should a breakthrough occur other antimalarials will have to be used for treatment, including mefloquine when it becomes more widely available.<sup>15</sup>

Primaquine, normally used for preventing relapses in *P vivax* malaria, should be avoided or used with great caution in any pregnant woman with a risk of deficiency of glucose-6-phosphate dehydrogenase. There is no evidence that chloroquine chemoprophylaxis causes any toxic effects on the eye or any congenital defects when given at the standard adult dosage of 300 mg base a week for as long as four to five years.<sup>17</sup> Adverse effects of chloroquine on the auditory system of the newborn were reported when the drug was given in very high dosage to pregnant women with rheumatoid arthritis and similar diseases. No such effects have been reported from malaria prophylaxis.

Like most of the other antimalarial drugs chloroquine crosses the placenta and appears in small amounts in maternal milk,<sup>10</sup> but this does not provide a full safeguard for the newborn baby, and the time honoured methods of protection from mosquito bites (bed nets, space sprays, and so on) need to be used.<sup>3</sup>

Finally, a traditional and usually unwelcome piece of advice given to any woman in her second half of pregnancy is to forgo any exotic travels unless unavoidable.

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## A cooler look at lead

"The things we would like to know may be unknowable, so there is some virtue in just getting rid of the problem," said Sir James Gowans, commenting on the issue of lead and intelligence at the end of a conference on lead held in Cardiff last week. Organised by the Medical Research Council Epidemiology Unit and the area postgraduate organiser, this meeting came in the wake of the Royal Commission on Environmental Pollution's report recommending the removal of lead from petrol.<sup>1</sup> Now that the Government's decision on petrol has put an end to this long and bitter controversy, a cooler look can be taken both at the scientific questions and at the other practical actions that are needed.

The royal commission reached its conclusion on grounds of prudence, without making any judgment about the evidence on the effects of low concentrations of lead on children's intelligence and behaviour. It was particularly worried that such a persistent and widely distributed toxin as lead should have so narrow a safety margin, but its conclusions were "not dependent on the precise accuracy of any particular investigation or calculation." This approach is welcomed by the *BMJ*, which has for some time urged the abolition of lead from petrol while remaining agnostic about some of the scientific evidence.<sup>2</sup>

Nevertheless, the effects of low concentrations of lead on children are still relevant to the urgency and the extent of the various practical actions recommended by the royal commission. In the last session of the Cardiff conference Marjorie Smith reviewed the evidence, including the Institute of Child Health and Southampton University study with which she was concerned and two others reported recently at the British Psychological Society's annual conference in York. The first of these three studies, on tooth lead in 6-7 year old London children, is the most extensive and detailed yet carried out. On the IQ scales and the reading test there were significant differences between the "high," "medium," and "low lead" groups; but after social variables were allowed for the differences became non-significant. The other two recent studies similarly showed differences in performance favouring children with the lower lead burdens but these too turned out to be non-significant.

What are we to make of these findings, taken in conjunction with the more positive earlier reports (reviewed in a recently published symposium<sup>3</sup>)? All the trends are in the same direction, and Marjorie Smith did not believe that they could be attributed to chance. Nevertheless, since controlling for all social variables was impossible the differences could well have resulted from social factors rather than differences in body burdens of lead—and if there was in truth a "signal" due to lead, she concluded, it might be undetectable amidst the "noise" of other factors. Rutter has presented arguments for accepting that the trends do represent a genuine though small effect of lead; and he makes two further important points—that an average reduction in IQ of only a few points in any group of children implies more damaging impairment in some of them, and that a given dose of lead may possibly do more harm to the socially disadvantaged children.<sup>3</sup>

Wherever the truth lies, there is a strong enough possibility of risk to justify energetic measures against lead exposure of all kinds. Lead in water still needs action.<sup>1</sup> Replacement of lead pipes gives a dramatic fall in both water and blood lead concentrations<sup>4 5</sup> but it costs some £600 a house and the work proceeds slowly. But for once the cheap solution begins to look like the superior one, and P C Elwood discussed the arguments