Malaria infections in pregnancy are associated with distinct epidemiological, pathophysiological, and clinical features, including a greater risk of complications during the acute course of the illness and adverse outcomes for both the mother and her child.2,3 Hyper-reactive malarial splenomegaly (HMS; historically known as Tropical Splenomegaly Syndrome [TSS] or “Big Spleen Disease”) is one of the most common causes of a markedly enlarged spleen in malaria-endemic regions, whereas uncomplicated malaria and schistosomiasis are common causes of splenomegaly.2,3 HMS is thought to represent an abnormal polyclonal B-cell-mediated response to recurrent or chronic malaria infection,5–7 which results in marked splenomegaly and functional hypersplenism.5 Although there is no single diagnostic test, cases can be identified using a defined set of clinical, laboratory, and histological criteria including gross splenomegaly (spleen size ≥ 10 cm below the costal margin), elevated immunoglobulin M (IgM) titers (often defined as ≥ 2 SD above the local mean), the presence of high titers of anti-malarial antibodies, evidence of a lymphocytic hepatic sinusoidal infiltrate on liver biopsy, absence of evidence of a neoplastic lymphoproliferative disorder, and a reduction in spleen size (≥ 40% over 6 months) in response to effective anti-malarial treatment.8 HMS is more common in certain ethnic groups (e.g., 80% prevalence in some tribes in New Guinea), and the association of severe HMS with HLA-DR2 is further evidence in support of an underlying host predisposition.9 Treatment consists of prolonged courses of effective anti-malarial therapy. Reduction in splenic mass is associated with a reduction in serological parameters.10,11

There are few data in the literature addressing HMS in pregnancy,2,3,12 which is of particular relevance given the susceptibility of pregnant women to malaria, the risk of splenomegaly in pregnancy in terms of anemia, thrombocytopenia, and increased susceptibility to infection, and the anxiety related to the safe administration of anti-malarial medication to pregnant women. This retrospective analysis aimed to characterize the effects of mefloquine treatment on spleen size and maternal IgM, IgG, and anti-malarial antibodies in pregnant women with splenomegaly in an area of low seasonal transmission on the Thai-Myanmar border.

This survey was undertaken at the Shoklo Malaria Research Unit (SMRU), Mae Sot, Thailand, between May 1994 and February 1997. Pregnant women were screened weekly for malaria by blood smear and every second week for anemia by hematocrit. Spleen size measurement was part of the routine obstetric examination. Any woman with significant splenomegaly (defined locally as ≥ 5 cm enlargement) and with a negative malaria film was given 5 mg/kg mefloquine weekly (Lariam, Roche Pharmaceuticals, Basel, Switzerland) as part of standard clinical practice to reduce anemia. A venous blood sample (3 mL) was sent to the Mae Sot Hospital for hemoglobin electrophoresis for detection of β-thalassemia (no test was available for α-thalassemia at that time). If during subsequent follow-up the spleen became impalpable, treatment was given for a further 2 weeks and then stopped; if the splenomegaly was unresponsive, treatment was stopped at 12 weeks. Women were followed up to delivery and neonatal outcomes were recorded.

Thirty-six women with suspected HMS were identified and treated as described; residual plasma samples from routine blood counts were stored for 31 of these women at the time of diagnosis and each time the woman was followed up. These samples were taken as part of routine clinical care. One hundred and twenty-nine samples (median samples per individual interquartile range [IQR]: 5 [3–6]) were processed for total IgM and IgG (Minineph, The Binding Site, Birmingham, UK); anti-malarial antibody titers (ELISA, DiaMed, Switzerland) were measured in a smaller subset of 87 samples taken from 23 cases (median samples per individual [IQR]: 4 [3–5]; mean value for duplicate tests obtained on 57 samples). Single samples taken from 29 malaria-smear negative pregnant women without splenomegaly from the same geographical area, population, and collected within the same time frame, were used as unmatched controls; total IgM and IgG were measured on all of these samples, and anti-malarial antibodies in a subset of five (mean value for duplicate tests obtained on all samples).

Concomitant rates of splenomegaly in the 3,503 women enrolled to antenatal care during the same period were 3.8% (134) for splenomegaly of any size and 1.0% (36) for splenomegaly ≥ 5 cm. By contrast, from May 2007 to September 2010 these proportions had dropped markedly to 0.5%

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falciparum Plasmodium ponded with a reduction in the incidence (69 of 12,067) and 0.3% (40), respectively; which corres-
totosis, normal lymphocyte response to phytohemagglutinin
index values were 9.1 (95% CI 8.1
CI 11.5
linear regression: co-efficient
index for cases were significantly higher than controls for all mea-
providing per woman. Pre-mefloquine treatment plasma titers
³
tion
of blood samples were available, 7 (23%) had splenomegaly
³
women: 4 (0
³
women) with hemoglobin-E disease (N
³
women with splenic reduction
b
–
0.001); total IgG was 17.6 (95% CI 15.9–19.3) versus 12.5 (95% CI 11.5–13.6) IU/mL, P < 0.0001; and anti-malarial antibody
index values were 9.1 (95% CI 8.1–10.2) versus 2.6 (95% CI 0.43–4.85), P < 0.0001. Significant reductions in spleen size
linear regression: co-efficient –0.14; SE 0.03; [95% CI –0.20–0.07]; P < 0.0001) and in anti-malarial antibody index
values (linear regression: co-efficient –0.69; SE 0.03; [95% CI –1.3–0.01]; P = 0.02) were observed with mefloquine treat-
ment. Decreases in IgM and IgG titers were also observed, although these did not reach statistical significance. Five
women had complete resolution of splenomegaly. Splenic
reduction (median [range]) was observed in women with and
without abnormal hemoglobin-typing (available for 30
women): 4 (0–8) cm with normal hemoglobin typing (N = 16), 2.5 (1–6) cm with homozygote β-thalassemia (N = 4); 3 (1–7) cm with β-thalassemia trait, N = 9; and no change in one with hemoglobin-E disease (P = 0.381). The proportion of
women with splenic reduction ≥ 40% was 75% (12 of 16) of
women with normal hemoglobin typing and 57.1% (8 of 14)
of women with abnormal hemoglobin typing, P = 0.442.

Women with suspected HMS were significantly older and
of higher gravidity, with a mean age of 30 versus 24 years (P = 0.0009) and 5 versus 3 pregnancies (P = 0.019), and on aver-
age, had a 17% proportional reduction in hematocrit at the
start of antenatal screening than contemporary controls:
28.8% (95% CI 26.6–31.0%) versus 34.8% (95% CI 33.3–
36.4%; P < 0.0001). The mean hematocrit before delivery in
women treated with mefloquine (5 mg/kg/week) increased to
31.5% (95% CI 26.6–31.0%; P = 0.05) from baseline, whereas
the hematocrit values in control women fell significantly to
32.6% (95% CI 31.2–34.0%; P = 0.009). There was no differ-
eence in mean birth weights between the two groups: 2,910 g
(95% CI 2,704–3,118 g) in cases versus 2,989 g (95% CI
2,856–3,123 g; P = 0.50) in controls. One baby in the group with
splenomegaly was born prematurely (< 37 weeks). All babies
in both groups had normal post-natal assessments (N = 50).

There are limitations to this retrospective analysis: the
sample size was small reflecting the relative rarity of HMS
in this population (prevalence 1%); the control group was
contemporary but unmatched; and there were no malaria
polymerase chain reaction data that have been used in other
settings to confirm low-density parasitemias in putative HMS
patients, thereby confirming active malaria infection as the
direct cause of splenomegaly. Other causes of splenomegaly
were also not explicitly ruled out, although there is no schis-
tosomiasis in the area, the rate of human immunodeficiency
virus and syphilis remains very low (< 0.4%), and none of
these women died of malignancy-related maternal deaths.
The raised anti-malarial antibody titer results presented here
are similar to a series of 50 Hmong refugees from Thailand
examined in Minnesota, North America, with a spleen > 2 cm.6
Despite these limitations, we show that in a group of women
with a spleen size ≥ 5 cm and negative malaria films, treat-
ment with mefloquine led to reduction in spleen size and
decrease in anemia, without any adverse outcomes. Splenic
reduction of ≥ 40%8 was also seen in women who did not
meet all the conventional criteria for HMS: in this analysis it
was a feature of 5 of 7 (71%) and 10 of 13 (77%) of women
with one and two major criteria of HMS, respectively; and
in women with abnormal hemoglobin typing. This suggests
that in a malarious area mefloquine is useful even when
splenomegaly is thought to be caused by hemoglobinopathy.

Total IgM and IgG titers were elevated in women with
splenomegaly, and anti-malarial antibodies were inevitably
present. Statistically significant decreases were not observed
in all of the serological parameters on treatment, perhaps
because of the relatively short period of follow-up (range for
last follow-up sample: 5–29 weeks). Weekly mefloquine can
be used for the treatment of HMS in pregnancy in areas
where P. falciparum parasites remain sensitive to the drug.

Received December 4, 2013. Accepted for publication January 1,
2014.

Published online March 3, 2014.

Acknowledgments: We thank the pregnant women who attended for
routine antenatal care and delivery and to the midwives, laboratory
and logistic staff who made this work possible.

Financial support: This work was supported by the Wellcome Trust
of Great Britain.

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Figure 1. Values of control and pre-mefloquine treatment
(for cases) total immunoglobulin M (IgM), IgG, and anti-malarial
antibody index results.
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