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Abstract. Dihydroartemisinin-piperaquine (DHA-PPQ) is a promising new artemisinin combination treatment. There are no published trials on fixed-dose ACTs in pregnant women in the second and third trimester of pregnancy; however, to date, Karen pregnant women with recurrent P. falciparum infections, despite 7-day treatments with quinine or artesunate (± clindamycin) or both, were treated with DHA-PPQ. This rescue treatment was effective and well tolerated and there was no evidence of toxicity for the mothers or the fetus. The PCR adjusted cure rate by Kaplan Meier analysis at day 63 was 92.2% (95% CI: 76.9–97.4).

INTRODUCTION

Multidrug-resistant Plasmodium falciparum malaria during pregnancy is an increasing public health concern in the tropics. Malaria infection—even if confined to asymptomatic parasitemia—is harmful for the mother and the fetus. In the border areas of Thailand, P. falciparum has developed resistance to all antimalarial drugs except the artemisinin derivatives. Studies from the North-Western border of Thailand have failed to find a significantly effective preventive measure for pregnant women. Quinine in pregnancy is associated with high failure rates; 30% of patients have polymerase chain reaction (PCR) confirmed recrudescences. Although efficacy can be improved by combining quinine with clindamycin, frequent side effects and the need for a 7-day course of treatment result in poor adherence. The World Health Organization (WHO) recommends the use of artemisinin combination therapy (ACT) (short-course, 3-day treatments) in the second and third trimester of pregnancy; however, to date published trials on fixed-dose ACTs in pregnant women include only 13 women. Mefloquine has been associated with an increased risk of stillbirth in Thailand and Artemether-lumefantrine is not widely used in this area. The only ACT available to us was DHA-piperaquine.

Dihydroartemisinin-piperaquine (DHA-PPQ) is a new co-formulated ACT effective against multidrug-resistant falciparum malaria. Both of the individual components have been used extensively in pregnancy, although exposure to DHA has mainly been as the metabolite of artesunate, and data on piperaquine from China, where it was the first-line drug for malaria for 16 years, are limited. Recent randomized clinical trials in Asia and Africa indicate excellent tolerability and high cure rates with DHA-PPQ. This new ACT is being used increasingly in South-East Asia, is already part of national treatment recommendations in Cambodia and Vietnam, and is being used to treat pregnant women in West Papua. Piperaquine (PPQ) is a “chloroquine-like” bisquinoline drug with a long half life and a favorable animal reproductive toxicity profile. We conducted a retrospective evaluation of pregnant women with multiple recurrent P. fal-

METHODS

Pregnant women in this case series attended the weekly antenatal care (ANC) of the Shoklo Malaria Research Unit (SMRU) on the North-Western border of Thailand. In this hilly forested area malaria transmission is low and seasonal. Acquired immunity is poorly protective and severe malaria is common at all ages, especially in pregnant women. At the start of the research program, maternal mortality due to malaria was high: 1,000 per 100,000 live births. Women are invited to come to the ANC as soon as they are aware of their pregnancy. All women attending the consultation are screened weekly for malaria as the only effective strategy to prevent maternal death. A PCR spot on filterpaper is done for each woman with P. falciparum malaria. Prophylactic ferrous sulphate (200 milligram/day), folic acid (5 mg/week), and vitamin B1 tablets (100 mg/day) are provided to all pregnant women on a weekly basis. Hematocrit levels are measured twice weekly and anemic women (hematocrit < 30%) are treated with ferrous sulphate (200 mg thrice daily) and folic acid (5 mg/day) and blood transfusion is given for symptomatic anaemia (hematocrit < 20%).

Treatment with 3 days of DHA-PPQ (DHA 40 mg, PPQ 320 mg per tablet, Holley Pharm PRC) was offered to women with recurrence of P. falciparum after 7-day regimens of quinine (± clindamycin), artesunate (± clindamycin), or both, who were then treated with dihydroartemisinin-piperaquine.

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were examined as soon as possible after birth and at 1 month of age.

Definitions used in the analysis include: febrile—(aural) temperature > 37.5°C; hyperparasitemia—≥ 4% red blood cells infected; anemia—hematocrit < 30%; severe anemia hematocrit < 20%; prematurity—delivery before 37 weeks gestation; low birth weight—infants with a birth weight of less than 2,500 g. Gametocyte carriage was defined as the number of weeks in which blood slides were positive for gametocytes, divided by the total number of weeks of follow up, and expressed per 1,000 person weeks.

Statistical analysis. Data were described using the statistical program SPSS for Windows (SPSS, Benelux Inc., Gorinchem, Netherlands) and Epi Info (Center for Disease Control and Prevention). The Kaplan Meier method was used to calculate parasitological efficacy.

RESULTS

In this retrospective analysis we report 50 Karen pregnant women with recurrent *P. falciparum* infections who were treated with DHA-PPQ between June 2006 and January 2007. The baseline demography of the women and total number of malaria episodes and treatments during pregnancy are summarized (Table 1). These 50 women had a total of 192 episodes of slide-confirmed malaria during their pregnancy: *P. falciparum* (N = 117), mixed (N = 13), and *P. vivax* (N = 62) malaria with a median [range] of 2 [2–8] episodes per pregnancy. Before the DHA-PPQ treatment 41 women received quinine (± clindamycin) and 14 artesunate (± clindamycin) treatments. Two women had an allergic reaction to quinine that necessitated a change to artesunate. The characteristics of the 62 episodes of malaria treated with DHA-PPQ are summarized (Table 2).

Safety and tolerability. All 62 episodes of malaria in all 50 women were included for this part of the analysis. No women deteriorated under treatment and no serious adverse events were reported. No women vomited any dose of DHA-PPQ. Of the 8 women with fever on admission all were afebrile by day 2. Parasite clearance occurred at a median [range] of 2 [1–5] days. Anemia on admission was present in 53.2% (33/62) of the episodes (Table 2). There were four episodes with severe symptomatic anemia that required blood transfusion (i.e., 8% [4/50]) of women. The day 28 hematocrit was significantly higher than on admission: mean SD [range] 30.7 ± 3.2% [22–38.0], P = 0.001 (paired t test).

Parasitological efficacy. Initial parasitological efficacy analysis was confined to the first rescue treatments in 47 women who completed the 3-dose course of DHA-PPQ. The 3 other women failed to complete treatment taking only a single dose. The median time to a negative smear was 2 [1–5] days. During 63-day follow-up there were 11 and 9 women who had *P. falciparum* and *P. vivax* reappearances at a median [range] of 49 [21–63] and 48 [35–63] days after starting treatment, respectively. PCR genotyping of recurrent *P. falciparum* infections identified 3 possible recrudescences: 1 definite identical genotype (day 21); 2 indeterminate (day 38 and 49), and 8 new infections. Thus assuming the indeterminate were in fact recrudescent infections (parasites can sequester in the placenta for months) the PCR-adjusted efficacy of morbidity and mortality in pregnancy. Over half the preg-
nant women in this retrospective series of acute uncomplicated *P. falciparum* malaria reported a history of fever or were febrile. There was a high rate of direct malaria-related adverse events: 8% of women had to be transfused in their second episode of *P. falciparum* malaria. Furthermore, 22% of babies were born with low birth weight, which increases the risk of death in the first weeks of life. This emphasizes the need for effective treatments in pregnancy. DHA-PPQ was used to rescue pregnant women with multiple recurrences of highly drug-resistant *P. falciparum* malaria. It proved effective and provided rapid fever and parasite clearance. Rapid resolution of symptoms reduces the risk of premature labor. Most recurrences were caused by new infections or by *P. vivax*. The PCR-confirmed cure rate and the median time to resolution of symptoms reduces the risk of premature labor. There were no serious adverse events related to the drug and the two abnormalities identified in the newborns are unlikely to be drug related. The pregnancy outcomes are similar to those of women treated for multiple infections with the combination of atovaquone-proguanil-artsunate for rescue treatment in pregnant women. As expected, the cure rates in these pregnant women with multiple malaria infections also appear lower than those achieved in non-pregnant patients from the same area with primary infections.

An effective, short-course, relatively inexpensive, fixed artemisinin combination has never been available to pregnant women on the Thai-Burmese border and DHA-PPQ currently looks the most promising candidate.

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