MAJOR ARTICLE

A Randomized Comparison of Artesunate-Atovaquone-Proguanil versus Quinine in Treatment for Uncomplicated Falciparum Malaria during Pregnancy

Rose McGready,[1,2,3] Elizabeth A. Ashley,[1,2,3] Eh Moo,[1] Thein Cho,[1] Marion Barends,[1,2] Robert Hutagalung,[1,2] Sornchai Looareesuwan,[2] Nicholas J. White,[2,3] and François Nosten[1,2,3]

[1]Shoklo Malaria Research Unit, Mae Sot, and [2]Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand; [3]Centre for Vaccinology and Tropical Medicine, Churchill Hospital, Oxford, United Kingdom

Background. There is no safe, practical, and effective treatment for pregnant women infected with multidrug-resistant *Plasmodium falciparum*.

Methods. We recruited pregnant Karen women in the second or third trimesters of pregnancy who had uncomplicated falciparum malaria for a randomized, open-label trial with a restricted sequential trial design of 7 days of supervised quinine (SQ7) versus 3 days of artesunate-atovaquone-proguanil (AAP).

Results. Eight-one pregnant women entered the study between December 2001 and July 2003; 42 were treated with SQ7 and 39 were treated with AAP. Fever, parasite clearance, and duration of anemia were significantly better with AAP; the treatment failure rate was 7 times lower (5% [2/39] vs. 37% [15/41]; relative risk, 7.1 [95% confidence interval, 1.7–29.2]; $P = .001$). There were no significant differences in birth weight, duration of gestation, or congenital abnormality rates in newborns or in growth and developmental parameters of infants monitored for 1 year.

Conclusion. AAP is a well-tolerated, effective, practical, but expensive treatment for multidrug-resistant falciparum malaria during the second or third trimesters of pregnancy. Despite the small number of subjects, our results add to the growing body of evidence that AAP is safe for the mother and the fetus.

Plasmodium falciparum infection during pregnancy has deleterious consequences for both mother and fetus; in low-transmission settings, it is potentially lethal [1]. There are few safe and effective therapeutic options during pregnancy. Concerns about fetal toxicity have caused researchers to exclude pregnant and lactating women from antimalarial drug trials. Quinine is considered to be safe during all trimesters of pregnancy, and it is widely recommended as a treatment, although adverse effects are common and adherence is poor. New drugs are needed, but the pharmaceutical industry is wary of developing them for use during pregnancy, given the fear of liability [2]. There is an urgent need to find suitable safe and effective short-course treatment options for pregnant women. Nowhere is the situation more serious than on the Thai-Burmese border, where *P. falciparum* has developed resistance to all antimalarials, with the exception of the artemisinin derivatives. In 1998, polymerase chain reaction (PCR) genotyping confirmed that the failure rate, assessed at day 63, after 7 days of supervised quinine (SQ7; 30 mg/kg/day) treatment in pregnant Karen women in this region was 33% (95% confidence interval [CI], 9.2%–56.7%) [3]. Artesunate has been used safely in >1000 pregnant women with resistant malaria in this area, but, either as monotherapy or combined with clindamycin, it has to be administered for 7 days. Artemisinin-based combination treatments (ACTs) are usually administered for 3 days, but partner drugs such as mefloquine are associated with safety concerns [4], and artemether-lumefantrine and dihydroartemisinin-piperaquine have not

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Reprints or correspondence: Dr. François Nosten, Shoklo Malaria Research Unit, PO Box 46, Mae Sot, Tak, Thailand 63110 (smru@tropmedres.ac).

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yet been evaluated during pregnancy [5]. Artesunate-atovaquone-proguanil (AAP) has proved to be a highly effective and well-tolerated treatment for multidrug-resistant falciparum malaria [6]. A preliminary noncomparative study conducted on a 3-day course of AAP in 27 women with multiple previous recrudescences of falciparum malaria showed high efficacy and no adverse effects for mothers or fetuses [7]. Subsequently, a pharmacokinetic study of AAP in another 27 pregnant women found no adverse effects, although patients had relatively low blood levels of atovaquone, proguanil, and dihydroartemisinin (the main metabolite of artesunate), which were approximately one-half the levels in comparable nonpregnant patients [8]. In the present article, we report a randomized trial of AAP versus SQ7 (the currently recommended treatment) to treat first episodes of uncomplicated but multidrug-resistant *P. falciparum* malaria during the second and third trimesters of pregnancy.

SUBJECTS AND METHODS

Study site and antenatal clinics (ANCs). The study was performed on the western border of Thailand in the ANCs of the Shoklo Malaria Research Unit (SMRU). ANCs were established in refugee camps in 1986 and in migrant-worker sites in Thai villages in 1998. Screening for malaria in weekly ANCs is the only proven method to prevent maternal death from malaria in this area [9]. Women were encouraged to attend ANCs for the detection and treatment of malaria by weekly blood-smear screening and checking of anemia by fortnightly hematocrit measurement and to receive routine hematinic (200 mg of ferrous sulfate 3 times daily and 5 mg of folic acid daily) and vitamin B1 (100 mg of thiamine hydrochloride daily) supplements [10]. Informed, written consent was obtained from all subjects. Approval for the study was obtained from the ethics committee of the Faculty of Tropical Medicine, Mahidol University, Bangkok, and the Oxford Tropical Research Ethics Committee.

Randomization and sample-size calculations. The study used a restricted sequential plan designed to detect a reduction in treatment failure from 30% in the SQ7 group to 5% in the AAP group ($\alpha = 0.05$ and $1 - \beta = 0.95$) [11]. Randomization was computer generated in blocks of 10, and treatment allocation was concealed in envelopes. Women were matched for study site (refugee or migrant) and for trimester of exposure (second or third).

Study participants. Otherwise healthy pregnant Karen women attending the SMRU ANC were invited to participate only if they presented with their first episode of uncomplicated falciparum or mixed (i.e., *P. falciparum* and *P. vivax*) infection and were in the second (>13 weeks) or early third (<32 weeks) trimester of pregnancy, had a hematocrit level ⩾20%, and were able to understand and adhere to the study protocol. Volunteers with known chronic disease (e.g., hemoglobinopathy or cardiac, renal, or hepatic impairment) or an inability to follow the ANC consultation, a history of alcohol abuse, imminent delivery, or an inability to tolerate oral treatment were excluded from the study.

At the time of enrollment, the purpose of the study was explained in the patient's own language. She was given a written explanation that was read to her if she was illiterate. It was made clear that refusal to participate at any stage would not alter in any way the quality of care provided. If consent was forthcoming, a full medical history and examination (including obstetric evaluation) was performed by a physician and a midwife. Complete blood count, hematocrit, and parasite count were measured, and blood group was determined. Thick and thin blood films were stained with Giemsa, and parasite density was expressed per 1000 red blood cells or per 500 white blood cells.

Drug regimens. Pregnant women received either quinine sulfate (Government Pharmaceutical Organization, Thailand) given 3 times daily (10 mg salt/kg every 8 h) for 7 days (SQ7) or 20 mg/kg/day of atovaquone, 8 mg/kg/day of proguanil, and 4 mg/kg/day of artesunate (AAP), each for 3 days. The fixed combination of atovaquone plus proguanil (Malarone) was dispensed as pink, film-coated tablets that each contained 250 mg of atovaquone and 100 mg of proguanil (GlaxoSmithKline). Each tablet of artesunate contained 50 mg artesunate (Guilin Factory No. 1). This is the same artesunate formulation that has been used effectively in extensive antimalarial drug trials at the same site [12]. Quinine was administered with a small amount of sugar mixed with water, and AAP was administered orally with 200 mL of chocolate milk (8% fat), to enhance absorption [13]. All drug administration was supervised, and personnel (except for laboratory technicians) were not blinded to the treatment group.

Management of recrudescent* P. falciparum *and* P. vivax *infections. Any woman with a reappearance of *P. falciparum* parasites after the primary drug treatment was retreated with 2 mg/kg/day of artesunate and 5 mg/kg of clindamycin 3 times daily, each for 7 days. Blood samples were obtained from women with parasite reappearance for in vitro sensitivity testing and PCR genotyping [14]. Episodes of *P. vivax* parasitemia were treated with chloroquine phosphate (25 mg base/kg for 3 days).

Monitoring for adverse events. Women were asked about adverse events on a daily basis for the first 3 days of treatment and then weekly until day 42. Possible adverse events were symptoms or signs that were not present at the time of admission but developed after the start of treatment but before the onset of subsequent parasitemia. The rates of each symptom (including those probably related to malaria) were compared between treatment groups. The rates of early vomiting (1 h) after each dose were also recorded.

Follow-up. During the treatment phase of the trial, pregnant women were admitted to the in-patient department of SMRU in Maela refugee camp or in Mawker Tai. Thereafter,

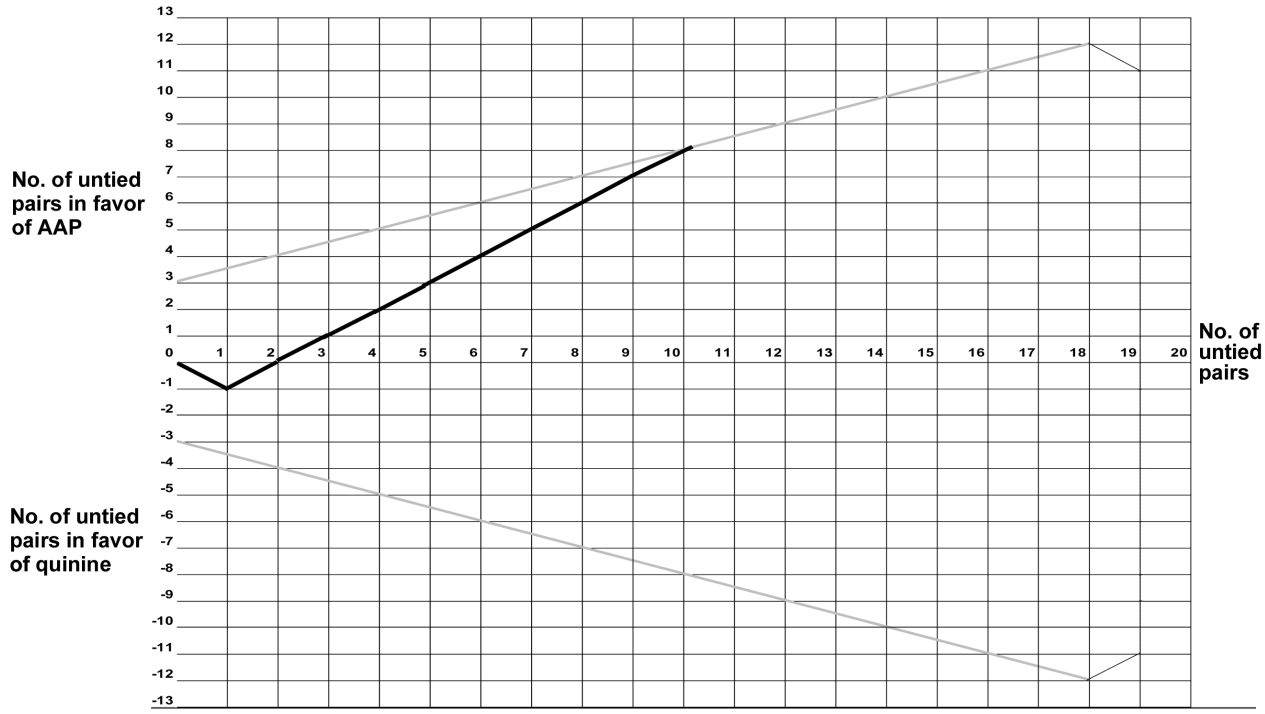

Figure 1. Excess of preferences, polymerase chain reaction–confirmed failures, in women treated with quinine, compared with those treated with artesunate-atovaquone-proguanil (AAP), in a random sequential trial of uncomplicated *Plasmodium falciparum* malaria in pregnancy. The upper and lower boundaries are calculated from the data of Armitage [11] and indicate limits of significance.

the women were seen weekly at the ANC. Parasitological follow-up continued for 9 weeks in total or until delivery, depending on which occurred later. If the woman was absent on day 63 but presented with a negative smear result until day 70 and had no history of self-treatment, she was assumed to be negative at day 63. Women in this area usually deliver at home with traditional birth attendants, but all women in the study were encouraged to attend the SMRU delivery suite in Maela refugee camp. Women who were identified antenatally as having an obstetric problem requiring caesarean section or other emergency treatment were referred to the local Thai government hospital. If home delivery occurred, infants were seen as early as possible after birth. Delivery details were recorded for all pregnancies, including sex, birth weight, arm circumference, head circumference, and height. Gestational age was estimated preferentially from ultrasound dating (if possible, at 18 ± 2 weeks), Dubowitz score at delivery, or fundal height, measured by use of the formula established for this population [gestational age (weeks) = fundal height (cm) × 0.887 + 4.968 [4], because few women had reported the date of their last menstrual period accurately. All infants seen before day 6 of life had a newborn neurological assessment and, where possible, were followed up at 1 week, 1 month, and monthly until they were 12 months old for growth and developmental monitoring. At 12 months of age, all infants underwent a full neurodevelopmental evaluation [15].

Definitions. Infants with a birth weight of <2500 g were defined as having low birth weight (LBW), and prematurity was defined as a gestational age of <37 weeks. Abortion and stillbirth were defined as the delivery of a dead fetus before and after 28 weeks, respectively. Anemia was defined as a hematocrit level of <30% and severe anemia was defined as a hematocrit level of <20%. The level of gametocyte carriage was only determined in women who did not have gametocytes at the time of admission. The number of person-gametocyte-weeks was calculated by dividing the number of weeks during which women had gametocytes after treatment by the number of weeks they were monitored and are expressed per 1000 person-weeks.

Statistical analysis. Data were described by use of the statistical programs SPSS for Windows (version 11; SPSS) and EpiInfo (version 6.40; Centers for Disease Control and Prevention). Categorical data were compared by use of the χ^2 test with Yates' correction or by Fisher's exact test. Continuous variables conforming to a normal distribution were compared by use of Student's *t* test. Data that were not normally distributed were log transformed or compared by use of the Mann-Whitney *U* test. Adverse events that were not present on day 0 were

Table 1. Admission characteristics of migrant and refugee pregnant women with *Plasmodium falciparum* malaria at the Thai-Burmese border, 2001–2003.

Characteristic	Treatment group		*P*
	SQ7	AAP	
Women in study	42	39	NA
Age, mean ± SD (range), years	26 ± 7 (16–39)	26 ± 6 (16–37)	.959
Weight, mean ± SD (range), kg	50 ± 7 (30–68)	49 ± 7 (40–69)	.759
Primigravida	11 (26.2)	12 (30.8)	.806
Splenomegaly	14 (33)	11 (29)	.812
Hepatomegaly	15 (35)	10 (26)	.474
Calculated EGA at entry, mean ± SD (range), weeks	21 ± 4.5 (14.9–30.2)	21 ± 5.3 (10.1–36.2)[a]	.977
History of fever at admission	31 (74)	23 (59)	.168
Anemia at admission, no./total no. (%)	19/42 (45.2)	15/39 (38.5)	.653
Parasitemia/μL,[b] geometric mean (range)	2084 (33–109,648)	2596 (33–123,027)	.664
Mixed infection	2 (4.8)	1 (2.6)	1.000
Presence of gametocytes	4 (9.5)	2 (5.1)	.677
Monitoring until parasite reappearance or day 63, median (range), weeks	6 (2–9)	9 (4–9)	<.001
No parasite reappearance	19 (46.3)[c]	34 (87.2)	NA
Novel infection	7 (17.1)[c]	3 (7.7)	
Recrudescent infection	15 (36.6)[c]	2 (5.1)	

NOTE. Data are no. (%) of women, unless otherwise stated. AAP, artesunate-atovaquone-proguanil; EGA, estimated gestational age; NA, not applicable; SQ7, 7 days of treatment with quinine.

[a] Two infants had an EGA determined at birth lower than that determined at the time of admission.

[b] Excludes women with mixed infection on day 0.

[c] Excludes 1 case of protocol violation and includes 1 woman whose second infection was reported as both new and recrudescent (i.e., $n = 41$ in the SQ7 group).

compared on days 1–2 and 7–42. Kaplan-Meier survival analysis with a log-rank test for significance was used to examine PCR-adjusted cure rates after treatment. Women who had new infections were included in the Kaplan-Meier analysis until the day they were retreated.

RESULTS

Baseline characteristics. Women were recruited between December 2001 and July 2003, when the boundary of significance for excess preferences in the restricted sequential trial was reached in favor of AAP (figure 1). At that time, a total of 81 women had been included: 39 had received AAP and 42 had received quinine. Three women, all in the SQ7 group but at different stages of pregnancy and at different sites, remained unpaired, because recruitment was halted before a suitable case was available. The 2 groups were comparable for clinical and laboratory variables measured at the time of admission (table 1).

Clinical and parasitological responses. Only 14 women (7 in each group) were febrile at the time of admission. All women treated with AAP cleared their fever by the second day of treatment, whereas 2 women in the SQ7 group cleared their fever on the third or fourth day of treatment. The median (range) time to parasite clearance was longer in the SQ7 group ($n = 40$), compared with that in the AAP group ($n = 39$): 4 days (1–7 days) versus 2 days (1–3 days), respectively ($P < .0001$). Overall, 28.6% (6/21) of quinine-treated women and 33.3% (12/36) of AAP-treated women developed *P. vivax* parasitemia during the 63-day follow-up period ($P = .7$).

Efficacy. Analysis of efficacy for the restricted sequential design was limited to unmatched pairs with complete follow-up data. The trial stopped when the boundary of significance for excess quinine failures was reached (figure 1). During the follow-up period, 27 episodes of *P. falciparum* malaria were detected by microscopy: 10 were caused by a new infection (7 in the SQ7 group and 3 in the AAP group), and 17 were recrudescent infections (15 in the SQ7 group and 2 in the AAP group). This gave a PCR-adjusted cumulative cure rate (95% CI) of 63.4% (46.9%–77.4%) (26/41) for SQ7 and 94.9% (81.37%–99.11%) (37/39) for AAP in the evaluable cases followed until delivery or day 63, whichever came last. The median (range) time to the PCR-confirmed parasite recrudescence for the 15 women in the SQ7 group was 21 days (13–49 days), whereas the 2 recrudescences in the AAP group occurred at 35 and 119 days. The median time from admission to a novel infection was longer (but not significantly so) in the AAP group, compared with the quinine group: 76 days (57–101 days) and 28 days (14–28 days), respectively ($P = .087$). Two women (5%) in the SQ7 group had an early treatment failure and failed to clear their parasitemia by day 7. In the SQ7 group, 86.7% (13/15) of those who failed to clear their parasitemia by day 3 had PCR-confirmed treatment failure (relative risk, 5.4 [95% CI, 1.4–20.3]). Most (27/28) second episodes of falciparum

Table 2. Birth outcomes for live-born singletons born to women treated with 7 days of quinine (SQ7) or artesunate-atovaquone-proguanil (AAP).

Characteristic	Treatment group		*P*	Both groups
	SQ7	AAP		
Birth weight, mean ± SD (range), g	2930 ± 648 (1000–4100) (*n* = 30)	2763 ± 550 (1750–3900) (*n* = 23)	.327	2856 ± 608 (1000–4100) (*n* = 53)
Percentage with low birth weight (<2500 g)	13.3 (4/30)	26 (6/23)	.299	18.8 (10/53)
Infant height, mean ± SD (range), cm	48.5 ± 3.8 (37–56)	48.1 ± 3.3 (39–54)	.715	48.3 ± 3.5 (37–56)
Head circumference, mean ± SD (range), cm	32.0 ± 2.6 (24–36)	32 ± 2.0 (28–36)	.813	32.0 ± 2.3 (24–36)
Mid–upper arm circumference, mean ± SD (range), cm	9.7 ± 1.4 (6–12)	9.4 ± 1.2 (7–11)	.536	9.5 ± 1.3 (6–12)
Estimated gestational age, weeks	38.8 ± 2.7 (29.1–43.2) (*n* = 38)	39.0 ± 2.0 (32–42.6) (*n* = 34)	.840	38.9 ± 2.4 (29.1–43.2) (*n* = 72)
Prematurity[a] (%) (no./total)	15.8 (6/38)	11.8 (4/34)	.740	13.9 (10/72)
IUGR, % (no./total)	7.4 (2/27)	12.0 (3/25)	.662	9.6 (5/52)
Congenital abnormality,[b] % (no./total)	2.6 (1/38)	5.9 (2/34)	.599	4.2 (3/72)

NOTE. IUGR, intrauterine growth retardation.

[a] Gestational age <37.0 weeks.

[b] One fetus showed left aural atresia at gestational age 29.0 weeks, and 1 fetus showed polythelia at gestational age 24.4 weeks and cleft lip and palate at gestational age 27.6 weeks.

Table 3. Growth and developmental parameters at 1 year of infant singletons born to women treated with 7 days of (SQ7) quinine or artesunate-atovaquone-proguanil (AAP).

Characteristic	Treatment group			
	SQ7 (n = 21)	AAP (n = 17)	P	Both groups (n = 38)
Weight, mean ± SD (range), g	8568 ± 1147 (7000–12,000)	8332 ± 814 (6850–9500)	.482	8463 ± 1006 (6850–12,000)
Height, mean ± SD (range), cm	72.1 ± 3 (67–79)	70.9 ± 4.1 (65–78)	.422	71.5 ± 3.7 (65–79)
Head circumference, mean ± SD (range), cm	44.4 ± 1.5 (41–47)	44.5 ± 1.3 (43–48)	.752	44.4 ± 1.4 (41–48)
Arm circumference, mean ± SD (range), cm	14.4 ± 1.3 (12–17)	14.1 ± 0.9 (12–15)	.315	14.3 ± 1.2 (12–17)
Sitting (range), months	6 (6–7)	6 (4–7)	.734	7 (4–6)
Crawling (range), months	7 (6–8)	7 (6–10)	1.00	7 (6–10)
Walking (range), months	12 (12)	12 (9–12)	.082	12 (9–12)
Total developmental score (range)	84 (74–90)	81 (76–89)	.198	83 (74–90)

malaria were treated with artesunate-clindamycin for 7 days (AC7 group). One woman, who had a premature delivery, was then treated with mefloquine and artesunate. Three of these women had third episodes of *P. falciparum* infection: 2 new infections and 1 PCR-confirmed treatment failure. These were all successfully retreated: 2 with a second course of AC7 and 1 with AAP.

Anemia. There was no significant difference in the mean hematocrit level between the groups at the time of admission or on any other days of follow-up (data not shown). From the time of enrollment until delivery, all but 5 women developed anemia, with no difference between groups in the proportion of women who became anemic: 92.9% (39/42) and 94.9% (37/39) in the SQ7 and the AAP groups, respectively. Women in the SQ7 group had a longer duration of anemia (expressed as a proportion of the pregnancy duration, in weeks) than women in the AAP group: 44.8% (224/500) versus 32.5% (152/468), respectively ($P < .001$). Four women in the SQ7 group developed severe anemia that required transfusion: 3 were for malaria-related anemia, and 1 was for an antepartum hemorrhage.

Gametocyte carriage. Of 81 women, 6 (7.4%) had gametocytes at the time of admission: 9.5% (4/42) in the SQ7 group and 5.1% (2/39) in the AAP group. The proportions of women who developed gametocytemia after treatment were 28.9% (11/38) and 5.4% (2/37) in the SQ7 and AAP groups, respectively ($P = .012$). The gametocyte carriage rate per 1000 person-gametocyte-weeks was 49 (95% CI, 26–89) in the SQ7 group and 6 (95% CI, 1–25) in the AAP group ($P = .003$).

Adverse events. There were no serious drug-related adverse events, and all women completed treatment without vomiting any doses of medication. There was no clinical deterioration of any women receiving treatment. One woman in the SQ7 group developed mild urticaria that responded to chlorpheniramine. She was able to complete the treatment protocol. There was 1 maternal death caused by a ruptured liver abscess. The 5 most common symptoms at the time of admission were headache in 71.6% (58/81), dizziness in 60.5% (49/81), muscle or joint pain in 59.3% (48/81), anorexia in 45.7% (37/81), and nausea in 29.6% (24/81), with no significant difference between the 2 groups. Monitoring for adverse events was discontinued in women with recurrent parasitemia (any species), so significantly more weeks of follow-up for adverse events were available for women in the AAP group (8 weeks [range, 5–9 weeks]), compared with women in the SQ7 group (5.5 weeks [range, 3–9 weeks]) ($P < .001$). Nevertheless, the only adverse effect that was significantly more frequent in 1 group was tinnitus in the SQ7 group: 79.3% (23/29), compared with 24.1% (7/29) in the AAP group ($P < .001$).

Delivery outcomes. Seven women (9%) moved and could not be monitored in ANCs until delivery. The remaining women (74/81 [91.3%]) delivered 73 singletons and 1 set of twins. Of the women whose deliveries were documented, 54.1% (40/74) occurred at the SMRU delivery suite, 37.8% (28/74) occurred at home, and 8.1% (6/74) occurred at the Thai Public Hospital. There was 1 stillbirth (estimated gestational age [EGA], 28 weeks) in the woman with a liver abscess, the day before her death, and the fetus was not weighed. The proportion of women who delivered at SMRU or at home was not significantly different between the SQ7 and AAP groups (data not shown). Body weight was measured in all live-born infants, but only singletons weighed within 24 h (73.6% [53/72]) were included in the analysis of birth weight. There was no significant difference in mean birth weight, baby growth parameters, and EGA or in the proportion of LBW, premature, or intrauterine growth–retarded infants (table 2). There were 3 infants born with congenital abnormalities in the study, and all of these were considered unlikely to be drug related (table 2).

Infant follow-up. All live-born infants (74), including 1 set of twins, were monitored monthly for growth and development. Of the 74 live-born infants, 5 died (6.8%), 10 (13.5%) could not be monitored up to 1 year of age because they left the study area, and 59 (79.7%) were followed up. Two of the 5

deaths occurred in premature infants (both born to women in the SQ7 group): 1 was triggered (on the third day of treatment) by a symptomatic *P. falciparum* episode and the other was triggered by a symptomatic urinary-tract infection. One infant born to a woman in the SQ7 group died of complications related to prolonged labor and birth asphyxia. Two infants born to women in the AAP group died of neonatal sepsis (1 case) and an unknown cause at age 2 months (1 case). Of the infants who could be monitored until age 12 months (78.0% [46/59]), 45 were alive and healthy (including the twins), and 1 was developmentally delayed. This infant, who was born to a woman in the AAP group who had an obstetric history of premature delivery, was premature (32.0 weeks) and had recurrent apneic episodes during the first month of life. The growth parameters, attainment of gross motor milestones, and neurodevelopmental scores were available for 38 infants (21 in the SQ7 group and 17 in the AAP group) and did not differ significantly between the treatment groups (table 3).

DISCUSSION

Quinine is very widely used in the treatment of falciparum malaria in pregnancy, but it is not well tolerated. It is bitter, it regularly produces symptoms of cinchonism, and it may cause serious hyperinsulinemic hypoglycemia. Adherence to the 7-day regimen required for maximum cure rates is poor, and, even in the unrealistic setting of supervised administration in this and earlier trials, more than one-third of women had a treatment failure. Potentially dangerous early treatment failures occurred in 5% of patients. A better treatment is needed. The present randomized trial clearly shows the superior efficacy of AAP over quinine for the treatment of uncomplicated multidrug-resistant *P. falciparum* malaria during the second and third trimesters of pregnancy. Treatment with quinine was less well tolerated and less efficacious, resulting in longer fever and parasite clearance times, a longer period of anemia, and a 7-times-higher rate of subsequent recrudescence than treatment with AAP. Longer parasite clearance times were predictors of subsequent treatment failure.

The considerably inferior efficacy of quinine may be explained, in part, by resistance in *P. falciparum* and, in part, by the pharmacokinetic properties of quinine during pregnancy. Quinine is still efficacious when it is combined with clindamycin, but this combination is not affordable in the region ($18 US/adult treatment). Replacing the effective, poorly tolerated 7-day quinine monotherapy for uncomplicated malaria during pregnancy in areas of multidrug resistance is complicated because there are no safe, effective, affordable, and practical alternatives. Tetracyclines are contraindicated during pregnancy, and the efficacy of azithromycin (promoted as a potential candidate for antimalarial use during pregnancy) has not been demonstrated in pregnant and in nonpregnant patients. Ideally, a well-tolerated, cost-effective 3-day ACT is needed. Artesunate plus mefloquine would be the logical choice, because it is safe and efficacious in nonpregnant patients, but mefloquine treatment has been associated with an increased risk of stillbirth in this population [4]. Artemether-lumefantrine is a potential candidate, but there are no published trials of its use in pregnancy, although the reproductive toxicological data are reassuring. Reproductive toxicological animal studies with dihydroartemisinin-piperaquine are in progress. Studies are urgently needed on the safety and efficacy, but also on the pharmacokinetics, of antimalarials (including quinine) during pregnancy, to optimize the dosage and to potentially improve therapeutic efficacy.

AAP was very well tolerated and highly effective; importantly, it was associated with a satisfactory birth outcome and infant development. The present study adds to the growing body of evidence that the artemisinin derivatives are safe when they are administered during the second and third trimesters of pregnancy. Studies of AAP in nonpregnant women have also shown very high cure rates. Earlier studies have shown reduced blood concentrations of dihydroartemisinin [16], atovaquone, and proguanil [8] during late pregnancy; despite this, the cure rate was >90%. Given the considerable intersubject variability in blood concentrations, this suggests a good margin of safety with current dosages of this combination. The treatment of uncomplicated recurrent *P. falciparum* infections in this area will continue to rely on artesunate (preferably in combination with clindamycin, if it is affordable). The triple, but even more costly, combination of AAP can be used in the most refractory cases.

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