Updated CDC Recommendations for Using Artemether-Lumefantrine for the Treatment of Uncomplicated Malaria in Pregnant Women in the United States

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Malaria infection during pregnancy is associated with an increased risk for maternal and fetal complications. In the United States, treatment options for uncomplicated, chloroquine-resistant Plasmodium falciparum and P. vivax malaria in pregnant women are limited to mefloquine or quinine plus clindamycin (1). However, limited availability of quinine and increasing resistance to mefloquine restrict these options. Strong evidence now demonstrates that artemether-lumefantrine (AL) (Coartem) is effective and safe in the treatment of malaria in pregnancy. The World Health Organization (WHO) has endorsed artemisinin-based combination therapies (ACTs), such as AL, for treatment of uncomplicated malaria during the second and third trimesters of pregnancy and is currently considering whether to add ACTs, including AL, as an option for malaria treatment during the first trimester (2,3). This policy note reviews the evidence and updates CDC recommendations to include AL as a treatment option for uncomplicated malaria during the second and third trimesters of pregnancy and during the first trimester of pregnancy when other treatment options are unavailable. These updated recommendations reflect current evidence and are consistent with WHO treatment guidelines.

Background

Each year, approximately 1,700 cases of imported malaria occur in the United States; approximately 630 (37%) of these cases occur in women, including 5%–6% who are pregnant at the time they are infected (4). Treatment options for uncomplicated, chloroquine-resistant P. falciparum and P. vivax malaria infections in pregnant women in the United States are threatened by the spread of mefloquine resistance in Southeast Asia. Having only one quinine and mefloquine manufacturer in the United States can adversely affect access. In 2009, the Food and Drug Administration (FDA) approved AL for the treatment of uncomplicated malaria. At that time, this combination was not approved for use in pregnancy because animal research data indicated a potential association with poor pregnancy outcomes, and insufficient human data were available. Since then, global experience has contributed substantial evidence of the safety and efficacy of AL throughout pregnancy. Given the need for an additional option to treat uncomplicated malaria in pregnant women in the United States, a systematic review of the literature was performed to evaluate the safety and efficacy of AL use during pregnancy, and findings were used to update CDC recommendations.

Methods

A systematic review of English-language research articles listed in PubMed was conducted using the keywords “artemether,” “lumefantrine,” “Coartem,” and “malaria in pregnancy.” Clinical trials, observational studies, meta-analyses, and case reports of uncomplicated malaria treatment during pregnancy were included. Studies that did not include treatment or pregnancy outcomes were excluded, as were studies that did not identify the trimester of treatment. Review article and meta-analysis references were examined for additional primary source articles for inclusion. Online search results were compiled and deduplicated. Two independent reviewers determined the relevance of each article to the research objective based first on title, then abstract, then full text. If reviewers had discordant findings from title or abstract review, the article was included in the next review phase. The following data were abstracted and reviewed: participant age; geographic location; parity; reason for drug treatment (uncomplicated versus severe malaria); trimesters during which treatment occurred; medication dose administered; treatment duration; treatment outcomes; and pregnancy outcomes, which included miscarriage (pregnancy loss at <28 weeks’ gestation), stillbirth (pregnancy loss at ≥28 weeks’ gestation), preterm birth (<37 weeks’ gestation), low birth weight (<2,500 g), congenital abnormalities, and any maternal adverse events reported.

Rationale and Evidence

Systematic review results. In the initial search, 1,726 articles were identified. After excluding four articles during deduplication, 1,534 during title review, 94 during abstract review, and 73 after full text review, 21 articles remained and were included in the review.

Efficacy. One meta-analysis (5) and five randomized open-label controlled trials performed in Uganda and Thailand examined the efficacy of ACTs for uncomplicated P. falciparum in women during their second and third trimesters of pregnancy and found cure rates ≥94.9%, with ACTs performing equal to or better than quinine-based regimens (Table 1) (6–10). A meta-analysis of African and Asian studies found lower but statistically similar treatment failure rates by days 28–63 in
women taking ACTs versus non-ACTs to treat uncomplicated malaria in the second and third trimesters of pregnancy (pooled risk ratio random effects = 0.41; 95% confidence interval (CI) = 0.16–1.06; six trials) (5). With respect to AL efficacy during the second and third trimesters of pregnancy, a concern existed that a reduction in relative bioavailability of lumezantrine in pregnant women might affect treatment success later in pregnancy (11–15). However, the evidence presented indicates that treatment in pregnancy is efficacious at the doses currently recommended for nonpregnant women.

Second and third trimester safety. Data evaluating pregnancy outcomes in women taking ACTs during the second or third trimesters of pregnancy were available from 16 studies (Table 2). No differences in pregnancy outcomes were identified in four trials comparing ACTs with quinine-based regimens in Uganda and Thailand (6,7,9,10), one of which used AL (9), and in four other trials comparing AL with other ACTs in Nigeria (two studies), Thailand, and multiple sites in Africa (16–19). A Zambian cohort study comparing treatment of uncomplicated malaria using AL with treatment using sulfadoxine-pyrimethamine found similar pregnancy outcomes between groups (20). In addition, two meta-analyses of women with malaria in the second and third trimester of pregnancy found no association between ACT treatment and congenital malformations or miscarriage (5,21). Overall, fewer maternal adverse events occurred among women taking ACTs than among those taking non-ACTs (Table 2). One trial in Thailand found a relatively higher proportion of day 7 anemia among those treated with mefloquine-artesunate (67%) than among those treated with a quinine-based regimen (42%) (6). Four trials and one meta-analysis comparing ACTs with quinine-based regimens found that pregnant women taking quinine had higher rates of tinnitus, dizziness, and vomiting than did pregnant women taking ACTs (5–9). The three trials comparing AL with other ACTs found no differences in rates of serious adverse maternal effects between groups (9,16,18).

First trimester safety. No randomized trials evaluating AL use during the first trimester of pregnancy were found (Table 3). However, a meta-analysis of observational and other studies from six sub-Saharan African countries and the Thai-Burmese border included data from a total of 717 women taking ACTs during the first trimester of pregnancy (22). Comparisons of pregnancy outcomes between women taking ACTs and those receiving a quinine-based regimen

### Table 1. Findings of randomized trials of artemisinin-based regimens for treatment of malaria in pregnancy

| Author, publication year | Country | Indication for treatment | Drug regimen | No. of participants | Follow-up time (days) | Treatment outcome, % (95% CI) |
|--------------------------|---------|--------------------------|--------------|---------------------|----------------------|-------------------------------|
| McGready, et al., 2000*  | Thailand| Uncomplicated *P. falciparum*, second and third trimesters | 1. MQ 25 mg/kg x 1 and As 4 mg/kg/d x 3d 2. Q 10 mg/kg q8hr x 7d | 66                    | 63                   | Cure 98.2 (94.7–100)†       |
|                         |         |                          |              | 42                   | 63                   | Cure 67.0 (43.3–90.8)†       |
| McGready, et al., 2001‡  | Thailand| Uncomplicated *P. falciparum*, second and third trimesters | 1. As 2 mg/kg/d x 7d 2. Q 10 mg/kg q8hr x 7d and CL 5 mg/kg q8hr x 7d | 64                    | 42                   | Cure 99.0                   |
|                         |         |                          |              | 65                   | 42                   | Cure 100                     |
| McGready, et al., 2005§  | Thailand| Uncomplicated *P. falciparum*, second and third trimesters | As 4 mg/kg/d x 3d and A 20 mg/kg/d x 3d and P 8 mg/kg/d x 3d | 39                    | 63                   | Cure 94.9 (81.37–99.11)†,***|
|                         |         |                          |              | 42                   | 63                   | Cure 63.4 (46.9–77.4)†,†††   |
| Piola, et al., 2010*     | Uganda  | Uncomplicated *P. falciparum* | 1. AL 20/120 mg 4 tabs at 0 and 8hr x 1d, then BID x 2d 2. Q 10 mg/kg q8hr x 7d | 152                   | 42                   | Cure 99.3 (96.0–99.9)†,†††   |
|                         |         |                          |              | 152                   | 42                   | Cure 97.6 (93.1–99.5)†,†††   |
| Kaye, et al., 2008†††     | Uganda  | Uncomplicated *P. falciparum*, second and third trimesters | 1. AL 20/120 mg 4 tabs at 0 and 8hr x 1d, then BID x 2d 2. LapDap x 3d | 57                    | 28                   | Cure 100                     |
|                         |         |                          |              | 57                   | 28                   | Cure 100                     |

**Abbreviations:** A = atovaquone; AL = artemether-lumefantrine; AQ = amodiaquine; As = artesunate; BID = twice daily; CI = confidence interval; d = days; hr = hour(s); kg = kilogram; LapDap = chlorproguanil-dapsone; mg = milligram; MQ = mefloquine; P = proguanil; PCR = polymerase chain reaction; Q = quinine; qd = once daily; q8hr = every 8 hours.

* McGready R, Brockman A, Cho T, et al. Randomized comparison of mefloquine-artesunate versus quinine in the treatment of multidrug-resistant *P. falciparum* malaria in pregnancy. Trans R Soc Trop Med Hyg 2000;94:689–93.
† PCR-adjusted.
‡ McGready R, Cho T, Koo NK, et al. Artemisinin antimalarials in pregnancy: a prospective treatment study of 539 episodes of multidrug-resistant *Plasmodium falciparum*. Clin Infect Dis 2001;33:2009–16.
§ McGready R, Ashley EA, Moo E, et al. A randomized comparison of artesunate-atovaquone-proguanil versus quinine in treatment for uncomplicated *falciparum* malaria during pregnancy. J Infect Dis 2005;192:846–53.
** 37 of 39 participants.
†† 26 of 41 participants.
†‡ Piola P, Nabasumba C, Turyakira E, et al. Efficacy and safety of artemether-lumefantrine compared with quinine in pregnant women with uncomplicated *Plasmodium falciparum* malaria: an open-label, randomised, non-inferiority trial. Lancet Infect Dis 2010;10:762–9.
** 137 of 139 participants.
††‡ 122 of 125 participants.
††† Kaye DK, Nshemerirwe R, Mutyaba TS, Ndeezi G. A randomized clinical trial comparing safety, clinical and parasitological response to artemether-lumefantrine and chlorproguanil-dapsone in treatment of uncomplicated malaria in pregnancy in Mulago hospital, Uganda. J Infect Dev Ctries 2008;2:135–9.
TABLE 2. Summary of studies using artemisinin-based treatment for malaria in second and third trimesters of pregnancy and safety outcomes

| Author, publication year | Indication (country) | Drug(s) | No. of participants | Pregnancy outcomes, n/N (%)* | Congenital anomalies, n/N (%) | Maternal adverse events, n/N (%) |
|-------------------------|----------------------|---------|---------------------|-----------------------------|-----------------------------|---------------------------------|
| McGready, et al., 2000†  | Uncomplicated *P. falciparum* (Thailand) | MQ 25 mg/kg x 1 and As 4 mg/kg/d x 3d | 66 | Miscarriage, 2 (3) Stillbirth, 0 (0) Low birth weight, 9/53 (17) | 0 (0) | Anemia day 7, 32/48 (67)§ Dizziness, (45)§ Tinnitus, (17)§ |
|                         |                      | Q 10 mg/kg q8hr x 7d | 42 | Miscarriage, 0 (0) Stillbirths, 0 (0) Low birth weight, 6/33 (18) | 0 (0) | Anemia day 7, 14/33 (42)§ Tinnitus, (66)§ |
| McGready, et al., 2001¶  | Uncomplicated *P. falciparum* (Thailand) | As 2 mg/kg/d x 7d | 64 | Stillbirth, 1 (2)** Minor, 1 (2) Tinnitus, (9) § | 0 (0) | Anemia day 7, 32/48 (67)§ Dizziness, (45)§ Tinnitus, (17)§ |
| McGready, et al., 2005††,§§ | Uncomplicated *P. falciparum* (Thailand) | As 4 mg/kg/d x 3d and A 20 mg/ kg/d x 3d and P 8 mg/kg/d x 3d | 39 | Preterm, 4/34 (12) Low birth weight, 6/23 (26) Stillbirth, 1 (2) | Polythelia and cleft lip and palate, 2/34 (6)** | Tinnitus, (24)§ |
|                         |                      | Q 10 mg/kg q8hr x 7d | 42 | Preterm, 6/38 (16) Low birth weight, 4/30 (13) Left aural atresia, 1/36 (3)** | Tinnitus, (79)§ |
| Piola, et al., 2010¶¶ | Uncomplicated *P. falciparum* (Uganda) | AL 20/120 mg 4 tabs at 0 and 8hr x 1d, then BID x 2d | 152 | Miscarriage, 2/144 (1) Intrauterine fetal death, 1/144 (1) Stillbirth, 2/144 (1) Preterm, 12/143 (1) Low birth weight, 12/120 (10) | Polydactyly, 2 (1)** Acanthotic heart disease, 1 (1) | Tinnitus, 0 (0)§ Headache, 26 (17)§ Nausea, 8 (5)§ Vomiting, 6 (4)§ Anorexia, 6 (4)§ |
|                         |                      | Q 10 mg/kg q8hr x 7d | 152 | Miscarriage, 2/137 (2) Intrauterine fetal death, 2/137 (2) Stillbirth, 3/137 (2) Preterm, 17/137 (3) Low birth weight, 16/137 (13) | Polydactyly, 2 (0)** | Tinnitus, 111 (73)§ Headache, 9 (6)§ Nausea, 26 (17)§ Vomiting, 28 (18)§ Anorexia, 16 (11)§ |
| Kaye, et al., 2008***   | Uncomplicated *P. falciparum* (Uganda) | AL 20/120 mg 4 tabs at 0 and 8hr x 1d, then BID x 2d | 57 | Not assessed | Not assessed | Palpitations, 4 (7) Dizziness, 1 (2) Drowsiness, 1 (2) Rash, 1 (2) Vomiting, 1 (2) Diarrhea, 1 (2) Palpitations, 1 (2) |
|                         |                      | LapDap x 3d | 57 | Not assessed | Not assessed | |

Randomized trials (open label unless otherwise noted) using artemisinin in comparison group

| Author, publication year | Indication (country) | Drug(s) | No. of participants | Pregnancy outcomes, n/N (%)* | Congenital anomalies, n/N (%) | Maternal adverse events, n/N (%) |
|-------------------------|----------------------|---------|---------------------|-----------------------------|-----------------------------|---------------------------------|
| Sowunmi, et al., 1998††† | Failed CQ, SP or CQ-SP treatment for *P. falciparum* (Nigeria) | Ar 3.2 mg/kg IM x 1 then 1.6 mg/kg IM qd x 4d Ar 3.2 mg/kg IM x 1 then MQ 7.5 mg/kg qd x 2d | 23 | IUGR, 1 | None | None |
| McGready, et al., 2008§§§ | Uncomplicated *P. falciparum* (Thailand) | AL 20/120 mg 4 tabs BID x 3d | 124 | Miscarriage, 0 (0) Stillbirth, 1/119 (1) | None | Vomiting, 2 (2) |
|                         |                      | As 2 mg/kg qd x 7d | 125 | Miscarriage, 1/122 (1)** Stillbirth, 1/119 (1) | None | Vomiting, 1 (1) Rash, 1 (1) |
| Ukah, et al., 2015¶¶¶ | Uncomplicated *P. falciparum* (Nigeria, double-blind) | AL (80 mg/480 mg) BID x 3d Ar-AQ (100 mg/270 mg) BID x 3d | 75 | Miscarriage, 1/71 (1) Low birth weight, 1/71 (1) | None | Vomiting, 2 (2) Diarrhea, 1 (2) Palpitations, 1 (2) |
|                         |                      | Ar-AQ (100 mg/270 mg) BID x 3d | 75 | Miscarriage, 1/71 (1) Low birth weight, 1/71 (1) | None | Vomiting, 2 (2) Diarrhea, 1 (2) Palpitations, 1 (2) |

See table footnotes on page 428.
### TABLE 2. (Continued) Summary of studies using artemisinin-based treatment for malaria in second and third trimesters of pregnancy and safety outcomes

| Author, publication year | Indication (country) | Drug(s) | No. of participants | Pregnancy outcomes, n/N (%)* | Congenital anomalies, n/N (%) | Maternal adverse events, n/N (%) |
|--------------------------|----------------------|---------|---------------------|-----------------------------|-------------------------------|--------------------------------|
| **PREGACT, 2016****,§§§§§ | *P. falciparum* (four African countries) | AL | 880 | Miscarriage, 1 | Stillbirth, 16/856 (2) | Preterm, (10) | Any defect, 17/832 (2) |
| | | AQ-As | 842 | Miscarriage, 4 (<1) | Stillbirth, 17/815 (2) | Preterm, (3) | Any defect, 8/776 (1) | Abdominal pain, 1 (<1) Malaise, 2 (<1) |
| | | MQ-As | 848 | Miscarriage, 4 | Stillbirth, 23/821 (3) | Preterm, (8) | Any defect, 13/780 (2) | Abdominal pain, 1 (<1) Vomiting, 2 (<1) Malaise, 1 (<1) |
| | DHA-PIP | 853 | Miscarriage, 4 (<1) | Stillbirth, 22/818 (3) | Preterm, (10) | Any defect, 6/767 (1) | Headache/weakness, 1 (<1) |

**Cohort study**

| Manyando, et al., 2010††††,§§§§ | Uncomplicated *P. falciparum* (Zambia) | AL 20 mg/120 mg 4 tabs BID x 3d | 495 | Miscarriage, 7/504 (1) (all first trimester exposures) | Stillbirth, 9/504 (2) | Preterm, 71/504 (14) | Any defect, 29/449 (7) | Not reported |
| | | SP (1500 mg/75 mg) | 506 | Miscarriage, 8/516 (2) (in 5 women, including one with twins and one with triplets) | Stillbirth, 13/516 (3) | Preterm, 90/516 (17) | Any defect, 18/444 (4) | Not reported |

**Descriptive studies (includes pharmacokinetic studies and case series)**

| McGready, et al., 2001† (includes data published 1998)**** | *P. falciparum* or mixed, primary and recrudescent, uncomplicated and severe (Thailand) | As given 2–4 mg/kg up to 7 days (varies by indication) or As 4 mg/kg qd x 3d and AP or As 4 mg/kg qd x 3d and MQ Community (no treatment) | 461 | Miscarriage, 20/414 (5) | Stillbirth, 7/386 (2) | Major 1/386 (1) | No serious adverse events |
| Mosha, et al., 2014**** | Uncomplicated *P. falciparum* (Tanzania) | AL 20/120 mg 4 tabs at 0 and 8hr x1d, then BID x 2d | 35 | Not assessed, (follow-up to 42 days only) | Not assessed | No serious adverse events |
| Nyunt, et al., 2015†††† | Uncomplicated *P. falciparum* (Uganda) | AL 20/120 mg 4 tabs at 0 and 8hr x 1d, then BID x 2d | 30 | Not assessed, (follow-up to 42 days only) | Not assessed | No serious adverse events |
| Adam, et al., 2004§§§§§,¶¶¶¶¶ | *P. falciparum* (Sudan) | Ar 80 mg IM BID x1d then qd x 2d | 28 | Miscarriage, 0 (0) | Stillbirth, 0 (0) | Premature, 1 (4)** | Not assessed |
| Adam, et al., 2009†††††,§§§§ | *P. falciparum* (Sudan) | Ar IM As and SP AL | 62 | Miscarriage, 2 (3)** (both had received artemether injections early in pregnancy and miscarried while receiving quinine infusions for a second malaria infection) | Not assessed | Not assessed |
| Wang, 1981††††† | “*Plasmodium*” (China) | Ar in oil 500–900 mg IM qd x 3d or Ar 600 mg IM qd x 3d | 6 | Miscarriage, 0 (0) | Stillbirth, 0 (0) | Premature, 0 (0) | Any defect, 0 (0) | Not assessed |

See table footnotes on page 428.
McGready R, Brockman A, Cho T, et al. Randomized comparison of mefloquine-artesunate-proguanil versus quinine in the treatment of multidrug-resistant falciparum malaria in pregnancy. Trans R Soc Trop Med Hyg 2000;94:689–93.

§ Significant difference between comparison groups.

McGready R, Cho T, Keo NK, et al. Artemisinin antimalarials in pregnancy: a prospective treatment study of 539 episodes of multidrug-resistant Plasmodium falciparum. Clin Infect Dis 2001;33:2009–16.

** Considered not related to drug.

†††††† Adam I, Elhassan EM, Omer EM, Abdulla MA, Mahgoub HM, Adam GK. Safety of artemisinins during early pregnancy, assessed in 62 Sudanese women. Ann Trop Med Parasitol 2008;102:771–6.

¶¶¶¶ Mosha D, Mazuguni F, Mrema S, Sevene E, Abdulla S, Genton B. Safety of artemether-lumefantrine exposure in first trimester of pregnancy: an observational study in Zambia. Malar J 2015;14:177.

†††† PREGACT Study Group. Four artemisinin-based treatments in African pregnant women with malaria. N Engl J Med 2016;374:913–27.

‡‡‡‡‡‡ Adam I, Elhassan EM, Omer EM, Abdulla MA, Mahgoub HM, Adam GK. Safety of artemisinins during early pregnancy, assessed in 62 Sudanese women. Ann Trop Med Parasitol 2009;103:205–10.

§§§§ Wang TY. Follow-up observation on the therapeutic effects and remote reactions of artemisinin (Qinghaosu) and artemether in treating malaria in pregnant woman. J Tradit Chin Med 1989;9:28–30.
### TABLE 3. Summary of safety outcomes in studies using artemisinin-based treatment for malaria in first trimester of pregnancy

| Author, publication year | Description or indication (country) | Drug or regimen (no.) | Pregnancy outcomes, no. (%) (unless otherwise indicated)* | Congenital anomalies, no. (%) (unless otherwise indicated) | Maternal adverse events, no. (%) (unless otherwise indicated) |
|-------------------------|-------------------------------------|-----------------------|----------------------------------------------------------|----------------------------------------------------------|----------------------------------------------------------|
| **Meta-analysis**        |                                     |                       |                                                          |                                                          |                                                          |
| Dellicour, et al., 2017† | Included five observational studies (individual participant data from six sub-Saharan African countries, and aggregate data from Thailand) | Areg (717)             | Miscarriage: Areg versus Q: aHR = 0.73 (95% CI = 0.44–1.21) | As 1.5% (95% CI = 0.6–3.5); Q 1.2% (95% CI = 0.6–2.4)    | C 66/408 (1.7); Q 48/294 (1.6)                               |
|                         |                                     | Q (947)               | Miscarriage: Areg versus none: aHR = 1.16 (95% CI = 0.81–1.66) |                                                          |                                                          |
|                         |                                     | No antimalarials (28,954) | Miscarriage and stillbirth: Areg versus Q: aHR = 0.58 (95% CI = 0.36–1.02) |                                                          |                                                          |
| **Observational studies** |                                     |                       |                                                          |                                                          |                                                          |
| Any anomaly, 1 (1)      | Identified women with inadvertent use of AL, other antimalarials, or none, then followed to birth outcome (Tanzania) | AL (164)               | Miscarriage, 5 (3) and stillbirth, 6 (3.7); Low birth weight, 8 (5.2); Preterm, 8 (5.2); aOR = 1.2 (95% CI = 0.6–2.5, p = 0.573) | Not assessed                                             |                                                          |
| Any anomaly, 2 (3)      |                                       | Q (70)                | Miscarriage, 3(4.3) and stillbirth, 5 (7.1); aOR = 2.5 (95% CI = 1.3–5.1, p = 0.009) |                                                          |                                                          |
| Any anomaly, 1 (1)      |                                       | SP (66)               | Miscarriage, 0 and stillbirth, 2 (3.0); Low birth weight, 2 (3.1); Preterm, 7 (10.9); aOR = 1.8 (95% CI = 0.8–4.1, p = 0.160) |                                                          |                                                          |
| Any anomaly, 1 (1)      |                                       | AQ (11)               | Miscarriage, 0 and stillbirth, 0; Low birth weight, 0; Preterm, 0 |                                                          |                                                          |
| No antimalarials (1,464)|                                       |                       |                                                          |                                                          |                                                          |
| Dellicour, et al., 2015** | Identified women with inadvertent use of AL, other antimalarials, or none, then followed to birth outcome (Kenya) | Confirmed ACT (77)     | Miscarriage: Confirmed ACT exposure only: Confirmed ACT 6/77 versus no antimalarial 57/793; aHR = 1.72 (95% CI = 0.66–4.45, p = 0.266) | Not assessed                                             |                                                          |
|                          |                                       | Unconfirmed ACT (222) |                                                          |                                                          |                                                          |
|                          |                                       | Q (13)                |                                                          |                                                          |                                                          |
|                          |                                       | No ACT exposure (835) |                                                          |                                                          |                                                          |
| Moore, et al., 2016††‡‡ | Data from antenatal clinics analyzed (Thai-Myanmar border) | Areg (183)            | Miscarriage: when compared with Q or Q and CL, Areg, 92 (11): aHR = 0.78 (95% CI = 0.45–1.34, p = 0.3645) | Any malformation: Uncomplicated Pf treated with Areg, 2/109 (2), Q, 9/641 (1), Severe Pf treated with: Areg, 2/22 (9); Q, 0/8 (0) |                                                          |
|                          |                                       | MQ (25)               |                                                          |                                                          |                                                          |
|                          |                                       | Q or Q and CL (971)   |                                                          |                                                          |                                                          |

See table footnotes on page 430.
are used to treat uncomplicated malaria in pregnant women, as well as population-specific disease burden; in addition, the FDA Adverse Event Reporting System maintains adverse event and medication error data, which can be used to monitor adverse events associated with AL use during pregnancy.

**Conflict of Interest**

No conflicts of interest were reported.

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