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REVIEW

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Antimalarial drugs for treating and preventing malaria in pregnant and lactating women

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ABSTRACT

Introduction: Malaria in pregnancy and postpartum cause maternal mortality and adverse fetal outcomes. Efficacious and safe antimalarials are needed to treat and prevent such serious consequences. However, because of the lack of evidence on fetal safety, quinine, an old and less efficacious drug has long been recommended for pregnant women. Uncertainty about safety in relation to breastfeeding leads to withholding of efficacious treatments postpartum or cessation of breastfeeding.

Areas covered: A search identified literature on humans in three databases (MEDLINE, Embase and Global health) using pregnancy or lactation, and the names of antimalarial drugs as search terms. Adverse reactions to the mother, fetus or breastfed infant were summarized together with efficacies.

Expert opinion: Artemisinins are more efficacious and well-tolerated than quinine in pregnancy. Furthermore, the risks of miscarriage, stillbirth or congenital abnormality were not higher in pregnancies exposed to artemisinin derivatives for treatment of malaria than in pregnancies exposed to quinine or in the comparable background population unexposed to any antimalarials, and this was true for treatment in any trimester. Assessment of safety and efficacy of antimalarials including dose optimization for pregnant women is incomplete. Resistance to sulfadoxine-pyrimethamine in *Plasmodium falciparum* and long unprotected intervals between intermittent treatment doses begs reconsideration of current preventative recommendations in pregnancy. Data remain limited on antimalarials during breastfeeding; while most first-line drugs appear safe, further research is needed.

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1. Introduction

Pregnant women are more vulnerable to malaria, leading to unfavorable impacts on the mother (maternal anemia and death), fetus (miscarriage, intrauterine growth restriction, stillbirth and preterm birth) or newborn (small for gestational age and perinatal mortality) even when asymptomatic [1]. Malaria is responsible for up to 20% of the maternal deaths in endemic areas [1]. Antimalarials are used not only for treating but also for preventing malaria infection in pregnant women. In both situations, the risk/benefit of toxicity of these drugs and clinical benefits need to be considered. This is particularly complicated in pregnancy as the long-term consequences of drug exposures in pregnancy and fetal outcomes need to be weighed up with potential under- or over-dosing due to the altered pharmacokinetics in pregnancy.

Embryotoxicity and teratogenicity are of special concern for any new drugs. For malaria, artemisinin derivatives are the current key antimalarial for non-pregnant patients. Since their introduction in 1990s, a dramatic decrease in the mortality as well as global prevalence of the disease has been documented. However, artemisinin is shown to be embryotoxic in animal studies [2,3]. As a consequence, quinine, an old drug with inferior efficacy and poor adherence, has continued to be recommended for women in the first trimester by the World Health Organization (WHO) [4]. There is recently, however, growing evidence on the safety of artemisinin in pregnancy including the first trimester [5,6].

As in pregnancy, rational use of medications for breastfeeding women requires consideration of benefits and risks for the mother as well as impact on infants of potential exposure to medications excreted in the breastmilk. Exposure is estimated through various calculated parameters, the most useful of which are the estimated dose to the infant (in mg of drug), and the relative infant dose (RID) – a weight adjusted percentage of the maternal dose that the infant would theoretically ingest. In general, RID of less than 10% is considered likely to be safe. However, various methods of calculating these parameters (for example, maximum concentration, average concentration, and area under the time-concentration curve have each been used to calculate dose to the infant) lead to heterogeneity of (limited) results between studies. In addition to these summary parameters, oral bioavailability, drug binding and safety of medications when directly administered to infants should be considered. Finally, the potential negative impact of interruption of breastfeeding needs to be weighed when making recommendations about the management of medications in lactating women. Advice to withhold breastmilk from the infant for a period of hours or days could have

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Article highlights

- Artemisinin derivatives are the most efficacious antimalarial ever and widely used except in pregnancy
- Animal studies have shown embryotoxicity and teratogenicity of artemisinin derivatives, but this was not shown in humans
- Quinine, the drug currently recommended in the first trimester, has lower efficacy and worse tolerability than the artemisinin-based therapies
- More evidence has been collected over the last two decades showing that artemisinin derivative use in any trimester in human pregnancy is not associated with increased risk of miscarriage, stillbirth or congenital abnormality compared to those who are treated with quinine, or to the background population level
- Prevention of malaria in pregnancy is challenged by widespread resistance to sulfadoxine-pyrimethamine and new strategies are needed to offer adequate protection from malaria infection without safety concerns for healthy pregnant women and their offspring
- Optimization of the doses of antimalarial drugs in pregnancy is needed to achieve adequate efficacy and safety for both treatment and prevention
- Pharmacokinetic and safety data on most antimalarials during breast-feeding is inadequate, but risk to the infant appears low for most first-line drugs, and should be considered in the context of the benefits of maternal treatment and maintenance of breastfeeding

This box summarizes key points contained in the article.

negative impacts, especially where safe breast milk alternatives are not available.

In this review, we summarize the recent evidence on the safety of currently used antimalarials in pregnancy and lactation, primarily in the context of treatment of falciparum malaria. A literature search was performed using three databases (MEDLINE, Embase and Global health) on human subjects. The names of each compound (artemisinin, artesunate, dihydroartemisinin, artemether, quinine, chloroquine, amodiaquine, lumefantrine, mefloquine, piperaquine, atovaquone, proguanil, sulfadoxine, pyrimethamine, clindamycin, primaquine or pyronaridine), 'pregnancy' or various terms for lactation, study types ('safe-' or 'pharmaco-') were used as keywords.

2. Quinine

2.1. Treatment in pregnancy

Quinine is given as a treatment (10 mg/kg/dose thrice daily for 7 days) with or without clindamycin. Quinine should be administered under full supervision because of poor adherence: about half of the patients treated with unsupervised quinine are estimated to fail treatment [7]. Pharmacokinetic studies indicated that increasing the oral quinine dose may be needed in pregnancy [8,9].

Quinine-based treatment showed lower efficacy, defined by polymerase chain reaction (PCR)-corrected adequate clinical and parasitological response (ACPR), than artemisinin-based treatment (pooled risk ratio [RR] of treatment failure 4.67, 95% confidence interval [CI] 1.60–13.67) in a meta-analysis [10] of five randomized control trials (RCTs) [11–15]. Parasite clearance was slower and the risk of gametocyte development after treatment was higher than artemisinin-based treatment [10]. The efficacy of quinine can be greatly improved by adding clindamycin [13], although other disadvantages of quinine cannot be overcome [10]. Quinine plus clindamycin, therefore, can be an option when artemisinin cannot be used (e.g. allergy), but special care (e.g. full supervision, and close clinical and parasitological monitoring with hospitalization) should be considered.

2.2. Acute adverse reactions

The adverse symptoms of quinine are collectively called cinchonism, which affects almost all patients [16]. This leads to poor adherence particularly among the pregnant women in the first trimester when morning sickness peaks. The actual adherence without supervision is thought to be poor [7]. The prevalence of tinnitus in pregnant patients on quinine is reported to be from 35% to 85% in > 450 patients assessed in seven studies [11–13,15,17–19]. A meta-analysis reported that the risks of tinnitus (pooled RR 4.70, 95% CI 1.20–18.39, five RCTs), vomiting (pooled RR 2.01, 95%CI 1.23–3.30, five RCTs) and dizziness (pooled RR 1.51, 95% CI 1.02–2.25, three RCTs) were higher than those of artemisinin-based treatment [10]. Nausea and anorexia are also more common with quinine than artemether-lumefantrine (AL) in an open-label RCT [12]. The risk of quinine related hypoglycemia is higher in pregnant women than the general population, particularly in cases with severe malaria [20,21]. For uncomplicated malaria, two studies reported that hypoglycemia was observed in 17% (4/24) [18] – 72% (21/29) [14], but symptomatic hypoglycemia was rare (0/246) [17]. To reduce side effects under-dosing treatment by prescribing twice daily dosing or only five days is potentially harmful and likely to induce resistance [7,18]. In a study in Uganda, QTc prolongation (Fridericia corrected QTc > 440 ms) was observed on day 2 in 1% (2/149) of the patients [12].

2.3. Impact on the fetus

Though historically used as an abortifacient, quinine is regarded as safe in the first trimester at therapeutic doses [4] and there was no evidence of an oxytocic effect on uterine contractions following quinine for severe malaria [20] or for uncomplicated malaria [13]. Studies on uninfected non-primate mammals showed embryotoxicity of quinine at doses equivalent to therapeutic doses for humans [22,23]. Teratogenic effects of quinine in humans were reported when it was used as an abortifacient (usually at toxic doses) [23], but there has been no clear evidence of fetal toxicity in humans when it is used for treatment.

A recent meta-analysis of five cohorts [6,24–29] including 947 pregnant women who were exposed to quinine in the first trimester reported higher risk of miscarriage (adjusted hazard ratio [aHR] 1.48, 95% CI 1.18–1.86, p = 0.001), but there was no difference in the risk of stillbirth (aHR 1.35, 95% CI 0.69–2.65, p = 0.39) and congenital abnormality (1.2%, 95% CI 0.6–2.4%) compared to those who were not exposed to any antimalarials [5]. The increased risk of miscarriage was considered to be related to malaria infection itself and was not different from those who were treated with artemisinin derivatives [5]. Two further observational cohort studies report the risk of

miscarriage after quinine exposure in the first trimester: 2.6% (1/38) in Papua New Guinea [30] and 3.8% (1/26) in Sudan [31]. The latter study reported no detectable congenital abnormality in infants followed up to 1 year (n = 26) [31]. Surveillance of Michigan Medicaid recipients between 1985 and 1992 reported that two cases with major congenital abnormality were observed (one expected) in neonates of 35 (5.7%) women who were exposed to quinine during the first trimester [23].

In the second and third trimesters, meta-analyses showed the risks of stillbirth and congenital abnormality are not different between quinine-based treatments and artemisinin-based treatments [10,32].

2.4. Use for breast-feeding women

No studies of quinine in breastfeeding women have been published in the last 20 years. A pharmacokinetic study from the 1930s reported that quinine is compatible with breastfeeding [33]. A 1986 study of 30 breastfeeding women in the first 10 days of lactation, found average breast milk concentrations after oral quinine were 3.4 mg/L leading to very low estimated drug exposure of less than 2–3 mg/day for most breastfed infants [34]. However, hypersensitivity reactions to quinine are not dose-dependent and could occur, though no reports exist in the literature of such a reaction occurring due to quinine exposure in breast milk.

One published report describes three neonates with G6PD-defiency-related hemolysis, which the authors attributed to quinine excretion in the breast milk from maternal ingestion of tonic water [35]. Though this is a possible explanation for the infants' hemolysis, the evidence for quinine as a G6PD hemolytic drug is weak [36] suggesting that other unidentified causes may have contributed.

Quinine should only be used in lactating mothers if other options are not available, and infant feeding and blood dextrose should be monitored closely during maternal treatment especially with intravenous dosing.

3. Artemisinin derivatives

3.1. Treatment in pregnancy

Artemisinin derivatives are the most effective antimalarials. For uncomplicated malaria, an artemisinin component, namely artesunate, artemether or dihydroartemisinin is given for three days (target dose of artesunate: 4 mg/kg/day) combined with drugs with a longer half-life (partner drugs). This is called artemisinin-based combination therapy (ACT). For severe malaria in any trimester of pregnancy, intravenous artesunate is the drug of choice [4]. Monotherapy of artemisinin is discouraged because of the risk of developing resistance to this important antimalarial [4]. Pharmacokinetic studies suggest increased dose of artemisinin in pregnancy may be needed [37–44].

The efficacy of artemisinins have not been assessed in the first trimester. In the second and third trimesters, a meta-analysis of five RCTs reported artemisinin-based therapy (including artesunate monotherapy) was more efficacious than quinine-based therapy (including quinine plus clindamycin) (pooled RR for treatment failure 0.21, 95% CI 0.07–0.63) [10].

3.2. Acute adverse reactions

Artemisinin derivatives are very well-tolerated in the general population without any serious adverse drug reactions [16]. Delayed hemolysis after artemisinin treatment has been infrequently reported especially in non-immune travelers and in individuals with severe malaria: an estimated 13% (95% CI 9–18%) of severe malaria cases receiving artesunate experienced hemolysis [45]. Neurotoxicity was extensively assessed in the 1990s and no evidence of neurotoxicity in humans was found after artemisinin treatment [16]. Allergy to artemisinins is estimated to affect 1 in 2833 patients (95% CI 1 in 1362 to 6944) [46], and has also been reported in pregnancy [13,47,48].

3.3. Impact on the fetus

Safety of artemisinin derivatives in the first trimester of pregnancy has been a concern because of embryotoxicity and teratogenicity (particularly musculoskeletal and cardiovascular defects) of artemisinin derivatives shown in animals, including one study on primates [2].

A recent meta-analysis assessed pregnancy outcomes of 717 pregnant women who were exposed to artemisinin derivatives in the first trimester [5]. The risk of miscarriage (aHR 0.73, 95% CI 0.44–1.21, p = 0.23), stillbirth (aHR 0.29, 95% CI 0.08–1.02, p = 0.053) and congenital abnormality (1.5%, 95%CI 0.6–3.5%) were not different from those who were exposed to quinine in the first trimester [5], even when the exposure was restricted to the embryo-sensitive period (6–12 gestational weeks) [5]. This meta-analysis of observational data suggests a non-statistically significant protection from early pregnancy loss with artemisinins compared to quinine for the treatment of malaria. This trend may be due to the better clinical and parasitological efficacy of artemisinin, as a falciparum malaria episode in the first trimester itself is associated with a 1.61-fold increase in the risk of miscarriage [6]. Proof would require a very large RCT in the first trimester, which is unlikely to ever take place.

Pregnancy outcomes have been described for an additional 259 women with first trimester artemisinin exposures [30,49–53]. In one report from Timika, west Papua, 11 women received ACTs and 10 received intravenous artesunate (for severe malaria) in the first trimester [30]. The prevalence of miscarriage was 63% (7/11) of those who received an ACT but 0 in those who received intravenous artesunate. No explanation was given for why these women received oral ACTs against the local treatment policy, and congenital abnormality was not assessed. The other studies did not report apparent excesses of adverse pregnancy outcomes in exposed women. Further 63 women in two studies were exposed to artemisinin in the first trimester, but no pregnancy outcomes were reported [54,55].

In the second and third trimesters, a meta-analysis of five RCTs reported that the risk of stillbirth (pooled RR 1.04, 95% CI 0.42–2.60) and congenital abnormality (pooled RR 1.29, 95% CI

0.40–4.17) after artemisinin-based treatment were not different from those who were treated with quinine-based treatment [10]. A meta-analysis of observational cohort studies reported no difference between the risks of miscarriage (pooled odds ratio [OR] 1.13, 95% CI 0.77–1.66, 3 studies), stillbirth (pooled OR 1.10, 95% CI 0.79–1.54, 4 studies) and congenital abnormality (pooled OR 0.79, 95% CI 0.37–1.67, 3 studies) in women exposed to artemisinins and those not exposed to any antimalarials [32].

3.4. Use for breast-feeding women

One conference abstract reports that negligible amounts (maximum concentration 35 ng/ml) of dihydroartemisinin were measured in breast milk after ingestion of a 200 mg dose of artesunate, but further details are not published [56]. The general tolerability of the artemisinins, combined with their short half-life and use in young infants suggest that the current practice of using artemisinins in breastfeeding women is safe.

4. Lumefantrine

4.1. Treatment in pregnancy

Lumefantrine is available as a fixed dose combination with artemether (480 mg lumefantrine plus 80 mg of artemether twice daily for three days) for treatment of uncomplicated falciparum malaria, recommended for the second and third trimester pregnant women by WHO. The US Centers for Disease Control and Prevention (CDC) has recently changed their recommendation and listed AL as an option for the first trimester women if neither mefloquine nor quinine plus clindamycin is available [57].

Lumefantrine blood concentration on day 7 was lower than non-pregnant populations in four cohorts [9,12,37,58–63], but was not different in one study [64]. Dose optimization by extending the length of treatment and/or increasing the dose was suggested by mathematical modeling [58,63,65], and assessed in two unpublished clinical studies [66,67]. Pharmacokinetics of a novel formulation of lumefantrine with increased bioavailability [68] need to be assessed in pregnancy.

Although the efficacy of AL was > 90% in most studies in pregnancy [10], some reports indicate the efficacy of AL for pregnant women can be lower than other artemisinin-based treatments at the currently recommended dosage [48,69].

4.2. Acute adverse reactions

AL is generally well-tolerated compared to other ACTs [69,70]. Early vomiting is rare and observed in < 0.4 [25] to 0.8% (1/125) patients [48]. Abdominal pain (28%, 43/152), headache (17%, 26/152), flu-like symptoms (16%, 25/152) were relatively common in an RCT in Uganda, but only headache was significantly more common with AL than quinine [12]. Abnormal biochemistries attributable to AL are rare in pregnancy [12,48,64,70,71]. No clinical cardiotoxicity was reported in two cohorts assessing electrocardiogram (ECG) in total 202 pregnant women treated with AL, with 2% (3/151) of QT prolongation (Fridericia corrected QT > 440 msec) recorded [12,37,48].

4.3. Impact on fetus

Of all ACTs, AL has the largest number of documented first trimester exposures. A recent meta-analysis of five cohorts [6,24–29] included 511 pregnant women who were exposed to AL in the first trimester, and no increased risk of miscarriage or congenital abnormality was reported (see above) [5]. Another observational cohort study reported three women exposed to AL in the first trimester without miscarriage or congenital abnormality [49].

In the second and third trimesters, the prevalence of stillbirth (1.9%, 16/856), preterm delivery (10.2%), low birth weight (17.2%) and congenital abnormality (2.0%, 17/832) were not different among ACTs in a multicentre RCT in Africa [69]. In another two RCTs including 250 patients in total, the prevalence of miscarriage, stillbirth, preterm, low birth weight and congenital abnormality after AL were not different from those after quinine [12] or artesunate monotherapy [48].

4.4. Use for breast-feeding women

There are no data on lumefantrine excretion in human milk. A conference abstract estimates the likely human exposure using a milk/plasma ratio derived from measurements in lactating rats, yielding an estimated exposure to the infant of 5.01 mg/kg, or an RID of 10% [72]. These findings are neither entirely convincing nor entirely reassuring and further studies in human milk for this fat-soluble drug would be helpful. As with all ACTs, there is limited data on use in neonates or infants < 5 kg. AL is a reasonable choice if treatment in lactating women is needed.

5. Amodiaquine

5.1. Treatment in pregnancy

Amodiaquine is used as a treatment for uncomplicated falciparum malaria in combination with artesunate. Artesunate-amodiaquine (ASAQ) is available either as fixed-dose or non-fixed dose combination, with amodiaquine 10 mg base/kg/day given once daily for three days. ASAQ is recommended in the second and third trimesters by WHO [4]. Limited data from 24 pregnant women in the second and third trimesters indicated there were no clinically meaningful pharmacokinetic changes in pregnancy [73,74].

There are only three studies assessing the PCR-corrected efficacy of ASAQ in pregnancy including around 750 women in the second and third trimesters in Africa [69,75,76]. PCR-corrected ACPR by day 28, 42 and 63 were all reported > 95% [10], although this high efficacy may not be achievable in Asia where resistance of amodiaquine is more prevalent [77].

5.2. Acute adverse reactions

In pregnancy, ASAQ is generally well-tolerated but associated with a higher risk of adverse symptoms than AL [69,70,78] or dihydroartemisinin-piperaquine (DP) [69,79]. Anorexia, nausea, vomiting, dizziness and weakness were more common than AL [69,70,78] or DP [69,79] and were more common in pregnant compared to post-partum women [73]. Weakness was particularly more frequent than other antimalarials [69,70,78–81]. Insomnia, behavioral change or hallucination were also reported [69]. Prolonged use of amodiaquine (as prophylaxis) is reported to be associated with increased risk of agranulocytosis and hepatitis [16], although clinically significant hematopoietic or hepatic toxicity is not reported after its short-term use as treatment in non-pregnant populations [16] as well as in pregnant women [69,70,73,75,76,80,82]. Hypotension was reported in 1.5% of the patients – more frequent than with other ACTs [69,73]. No QTc prolongation (> 500 msec) was observed in 83 pregnant women treated with ASAQ [75].

5.3. Impact on the fetus

Amodiaquine is considered safe in pregnancy as it is structurally similar to chloroquine [83], although its use in the first trimester has not been well documented. Three studies report birth outcomes with amodiaquine treatment of malaria before the 20th gestational week. In the first study, all 11 women gave full-term live-births without congenital abnormality [26]. In the second study, seven gave birth to full term live-births, one miscarried and one left before outcome was available [73]. In the third study, three women were treated with ASAQ and one of them miscarried [30].

In the second and third trimesters, the prevalence of stillbirth (2.1%, 17/815), preterm delivery (3.4%), low birth weight (15.5%) and congenital abnormality 1% (8/776) were not different from other ACTs [69]. In other RCTs assessing the pregnancy outcomes of 162 women, the risk of pregnancy loss was not different from those for AL [78] or DP [79].

5.4. Use for breast-feeding women

There are no data on amodiaquine use in breastfeeding women. Amodiaquine is used in infants (it is recommended for routine prophylaxis starting at 3 months in sub-Saharan Africa) [4] so use in women breastfeeding older infants may be acceptable. When possible, other medications should be used.

6. Mefloquine

6.1. Treatment in pregnancy

Mefloquine is used as a treatment for uncomplicated falciparum malaria in combination with artesunate. Artesunate-mefloquine (ASMQ) is available either as fixed-dose (440 mg mefloquine hydrochloride plus 200 mg artesunate once daily for three days) or non-fixed dose combination (mefloquine 25 mg/kg in total given for a course). ASMQ is recommended in the second and third trimesters by WHO [4].

Pharmacokinetic properties of mefloquine in pregnancy are not consistently reported across the literature [84–87]. Further studies are needed to assess whether dose optimization is necessary for pregnant women.

There are seven studies assessing the PCR-corrected efficacy of ASMQ (or artemether-mefloquine) in pregnancy including over 1000 women in the second and third trimesters [14,15,69,87–90]. PCR-corrected ACPR by day 63 was > 95% in all four studies that assessed PCR. The other three smaller studies including 65 pregnant women followed for 28 days reported no recurrences [14,88,89].

6.2. Acute adverse reactions

In pregnancy, ASMQ is generally well-tolerated for treatment of acute malaria episodes but associated with a higher risk of adverse symptoms than AL or DP [69] but lower than quinine [14,15,91]. An increased risk of anorexia, nausea, vomiting, dizziness and weakness compared to DP or AL was reported [69]. Early vomiting is frequent when mefloquine is given as a single dose [92], but this risk is mitigated by divided dosing, given after artesunate [15,16]. Early vomiting was observed in 9% (5/55) after the administration of fixed-dose combination [87]. Other distressing but uncommon adverse symptoms include behavioral change (1/850) and insomnia (2.5%, 21/850) [69]. These neuropsychiatric adverse symptoms have plagued military malaria prophylaxis programs and limit mefloquine use in severe malaria but appear to be uncommon with uncomplicated malaria treatment. They are reported to dose-dependent and seem to be different among different ethnicities [16]. Because of these adverse symptoms, mefloquine is contraindicated for the treatment after severe malaria and those who have a history of convulsion or psychiatric disorders. There were no cases with clinically significant hematological or biochemical abnormality reported in pregnancy [69,87–90]. Mefloquine is not regarded as cardiotoxic [16] and there was no cardiotoxicity recorded in a study assessing ECG of 60 pregnant women who received weekly mefloquine prophylaxis [93].

6.3. Impact on the fetus

Currently, US Food and Drug Administration (FDA) categorizes mefloquine as a pregnancy category B and US CDC recommends mefloquine monotherapy for the first trimester [57]. Although early clinical studies and animal studies suggested an increased risk of fetal loss after mefloquine exposure in pregnancy [22,23,93,94], subsequent clinical studies in pregnancy are reassuring. Post-marketing surveys among travelers in non-endemic countries who were exposed to mefloquine found no increased risk of pregnancy loss (10.3%, 112/1090) or congenital malformation (4.4%, 43/978) compared to the background population level even used in the first trimester [95–97]. On the Thailand-Myanmar border, the risk of miscarriage after the first-trimester exposure to mefloquine (8%, 2/23) was not different from that after quinine (11%, 92/750) [6].

In the second and third trimesters, in a multicentre RCT in Africa, the prevalence of stillbirth (2.8%, 23/821), preterm labor (7.7%), low birth weight (15.2%) and congenital abnormality

(1.7%, 13/780) after ASMQ were not different from other ACTs [69]. Another five studies assessed an additional 363 pregnant women (including 13 in the first trimester) exposed to mefloquine and reported three miscarriages, three stillbirths and two congenitally abnormal infants [15,89,90,92,98,99]. Neurodevelopment in exposed fetuses has not been studied.

6.4. Prevention

Mefloquine prophylaxis (250 mg weekly) is recommended by US CDC for pregnant travelers [100]. In the only double-blind placebo control trial published, mefloquine was found to be safe in Karen pregnant women living on the Thailand-Myanmar border [93]. The most common adverse effects (weakness, dizziness, anorexia, headache) were not different between the mefloquine and the placebo groups. Most of the more recent trials using mefloquine used the intermittent preventive treatment in pregnancy (IPTp) approach and these have been reviewed recently [101]. The main conclusions are that mefloquine was more effective than sulfadoxine-pyrimethamine (SP) in preventing malaria, but more adverse reactions were reported with mefloquine. It should be noted however that the doses used in these studies were not optimized to limit the occurrence of adverse reactions as suggested by numerous studies conducted in non-pregnant patients [102]. In addition, these studies were not 'double-blind', and it is likely that a bias was introduced in the tolerability assessment. As a result, the risk/benefit analysis is not favorable to use mefloquine as IPTp (higher doses than weekly prophylaxis) because on the one hand tolerability is poor with the regimen used (2–3 treatment doses during pregnancy) while on the other hand these regimens could not achieve protection against malaria and up to 4–12% of the women had placental malaria at the time of delivery [103].

6.5. Use for breast-feeding women

The current evidence supports the use of mefloquine in breast-feeding women, but there is uncertainty about exact level of infant exposure. The one published study of the pharmacokinetics of mefloquine in breast milk reported milk/plasma ratios of 0.16 and 0.13 in two volunteers over the first 4 days following a single 250 mg dose of mefloquine. The calculated RID of 3.8% is reassuring. Mefloquine has a long half-life and concentration in breast milk 56 days after administration had decreased only 40% from the concentrations on day 1 [104]. However, even prolonged exposure to these very low doses is unlikely to cause adverse events in breastfeeding infants.

Mefloquine is recommended for infants as low as 5 kg, but experience in young infants and neonates is limited [105]. Further studies would be valuable to clarify the amount of drug that a breastfed infant would be exposed to following maternal treatment with a typical three-day antimalarial treatment with mefloquine.

7. Piperaquine

7.1. Treatment in pregnancy

Piperaquine is used as a fixed-dose combination with dihydroartemisinin (960 mg piperaquine plus 120 mg dihydroartemisinin once daily for three days). DP is recommended as a treatment for the second and third trimesters by WHO [4]. Pregnancy is associated with a shorter terminal elimination half-life [43,44,106–108]. However, the impact of pregnancy on the area under the plasma concentration curve is inconsistent: with both increased [43,107] or decreased [108] results reported.

The PCR-corrected ACPR by day 63 is ≥ 95% in all studies [43,69,107] except one study reporting 92% following treatment of recurrent infection [109]. In one of them, the PCR-corrected ACPR was significantly higher than that of AL, but the difference was less than 5% [69].

7.2. Acute adverse reactions

DP is very well-tolerated [43,69,79,107–110] and adverse symptoms were fewer than ASAQ [69,79] and ASMQ [69]. Early vomiting was observed in 0.8% (2/245) of the pregnant women who received DP as treatment and 0.2% (4/1725) of the episodes given as IPTp [110]. QT prolongation was reported, but no associated clinical cardiotoxicity was reported [108,111–113].

7.3. Impact on the fetus

Reproductive toxicity of piperaquine was not shown in rats and rabbits [22,114]. The clinical use of DP in the first trimester has not been well documented [5]. A small number of women in an observational cohort miscarried after the treatment of DP in their first trimester (63%, 5/8), which was higher than quinine (2.6%, 1/38) [30]. It was not clear why these patients were treated with DP against the local health policy. Another three women who failed quinine treatment were treated with DP in the first trimester [109]. Among them, there were no stillbirths or congenitally abnormal newborns [109].

In the second and third trimesters, the prevalence of stillbirth (2.7%, 22/818), preterm labor (9.5%), low birth weight (14.1%), and congenital abnormality (0.8%, 6/767) were not different among different ACTs [69]. In two cohort studies that include > 100 patients, the risks of stillbirth after the exposure to DP mainly in the second and third trimesters were < 3% [30,79]. One RCT reported the risk of low birth weight was higher than ASAQ (13.2% (12/91) versus 4.2% (3/72); calculated RR 3.16; 95% CI 0.93–10.79; p = 0.048), but the authors concluded this could have been a chance finding [79]. The average birth weight was not different between two groups in this study.

7.4. Prevention in pregnancy

There are few studies on the use of DP for the prevention of malaria in pregnancy. The most common adverse reactions are vomiting (< 2%) and abdominal pain (< 3%). The drug is well-tolerated when given either as IPTp or as a monthly dose [112]. The frequency of administration and the dosing still need to be defined in order to assess the risk/benefit. The pharmacokinetics of DP do not support its use as a conventional IPTp regimen (like with SP) of 2–4 treatment doses in the second and third trimesters. The recent study by Desai *et al* demonstrated that IPTp-DP was as ineffective as IPTp-SP with over 30% of the women

positive for placental malaria at delivery [110]. A monthly regimen is more likely to have a favorable risk/benefit ratio as shown in non-pregnant subjects [115] and in one trial in pregnancy [112]. Mathematical modeling suggests that a weekly regimen (i.e. the prophylactic approach) would be most optimal for the prevention of malaria [116].

7.5. Use for breast-feeding women

One study evaluated piperaquine transfer into breastmilk of 27 lactating women who had received DP in their third trimester (mean 63 days before sampling) [117]. Piperaquine was still measurable in serum and breast milk in 24 of the 27 women, and serial samples were collected on the day after delivery and periodically until day 17. The average milk/plasma ratio was 0.63 across all measurements, and 2.5 at birth (reflecting the higher permeability of the blood-breastmilk barrier in the first few days of lactation). Daily infant doses were estimated at 0.41 µg/kg/day and RID was 0.004%. Mathematical modeling predicted the amount of piperaquine that neonates would be exposed to if mothers were treated while breastfeeding, with maximum total cumulative piperaquine exposure of 101 µg/kg corresponding to an RID of 0.11%. These very reassuring data make DP the most appropriate ACT choice for lactating women, when available. However, actual data on treatment in lactating women would strengthen this recommendation.

8. Atovaquone-proguanil

8.1. Treatment in pregnancy

Atovaquone-proguanil (AP) can be used as a prophylaxis in areas of chloroquine/mefloquine resistance and can be used as a treatment with or without artesunate [118], although it is currently not on the list of antimalarials recommended by WHO [4]. Pharmacokinetic studies indicate that increased dose of AP may be considered in pregnancy [119–122].

Four studies assessed the use of AP alone [120] or with artesunate [11,119,123]. Efficacy was more than 95% [11,119,120,123] on the Thailand-Myanmar border (n = 110) and in Zambia (n = 16), and was better than quinine monotherapy in an RCT [11]. The use of this drug in endemic countries was restricted because the resistance of atovaquone can be easily acquired by single point mutations of *cyt b* gene [124], although a recent study indicates that parasites with this mutation cannot survive in mosquitos, and thus the resistance cannot be transmitted [125].

8.2. Acute adverse reactions

AP is very well-tolerated in non-pregnant populations [16] and is regarded to be safe for pregnant women [4,23,83,124]. In a total of 126 pregnant women treated with AP [11,119,120,123], there were few adverse symptoms that could have been due to malaria itself [120] and whose risks were similar to those after artesunate alone [123]. No cardiotoxicity was reported in 24 patients assessed [119].

8.3. Impact on fetus

No teratogenic or embryotoxic effects were shown in rats and rabbits [126]. However, a theoretical concern on its use in the first trimester remains as cycloguanil, the active metabolite of proguanil, is an anti-folate. Co-administration of folic acid supplements at least during the first trimester should thus be considered [23]. In total 327 women were reported to be exposed to AP in the first trimester either as treatment or prophylaxis [123,127–129]. In the cohort of Danish travelers receiving AP as prophylaxis in their first trimester, the prevalence of congenital abnormality was 1.3% (2/149) and risk was not increased in comparison to that of the background population (2.5%, 13,993/570,728, odds ratio 0.55, 95% CI 0.14 to 2.21) [127]. Another cohort of travelers in Europe including 165 women exposed to AP either as prophylaxis or treatment in the first trimester reported 13% (12/165) of miscarriage and 4% (4/162) of congenital malformation [128]. The other 13 women exposed to AP in the first trimester delivered live-born babies without congenital abnormality [6,123,129].

After AP use as treatment in the second and third trimesters, one study reported two newborns with congenital abnormality (5.9%, 2/34) [11]. In the other three studies including 70 women, no newborns with congenital abnormality were documented [119,120,123]. No pregnancy loss was documented in around 100 women [11,119,120,123].

8.4. Use for breastfeeding women

No data are available on the excretion of atovaquone in human breast milk [126]. The manufacturer reports that proguanil is found in small quantities in human milk, but details are not available [126]. Because of the potential risk of adverse events in breastfed infants, use of this drug is discouraged in lactating women [23].

9. Sulfadoxine-pyrimethamine

Because of the widespread resistance to SP [130], it is no longer used for treating falciparum malaria in most of the world. Despite the resistance, SP (1,500 mg of sulfadoxine and 75 mg of pyrimethamine given as a single dose) is recommended for use by WHO in sub-Saharan Africa as IPTp [131]. The safety of IPTp-SP was extensively reviewed in 2007 [132] and the drug is generally considered to be safe in pregnancy. When administered at treatment doses 1–4 times during the second and third trimesters, the adverse effects are minor and infrequent. Higher doses of SP can be associated with megaloblastic anemia by antagonizing folate. But the most serious adverse reactions are Severe Cutaneous Adverse Reactions (SCAR). The rate of SCAR is reported to be 1/5000–8000 in travelers taking weekly prophylaxis with SP but it has not been reported in most studies using SP for IPTp, although in one study a woman with HIV died of SCAR after receiving an IPTp-SP dose [133]. SP (like other dihydrofolate reductase inhibitors) is teratogenic in animal studies and is not given to women in the first trimester. Because of the risk of neural-tube

defects by competition with folate, WHO recommends administering SP with a low dose folate (0.4 mg/kg) during pregnancy. Resistance to SP in *Plasmodium falciparum*, the intervals between doses that leave women unprotected and its contraindication in first trimester mean that the risk/benefit ratio is unfavorable for IPTp-SP and the current policy needs to be changed [134]. The pharmacokinetics of SP in pregnancy, completed a decade after WHO recommended it for IPTp every trimester, dictate that frequent (monthly) dosing is required to obtain adequate blood concentrations for prevention [135].

The WHO recommends against the use of SP in infants less than 2 months old or premature infants [4], and the manufacturer recommends against its use in women breastfeeding infants less than 2 months old. There are not enough data to confidently assess the safety of SP in breastfeeding women.

The most recent study of pyrimethamine excretion in breast milk, published in 1986, found an average of 0.23 mg of the drug in the breast milk of three lactating volunteers over 9 days following a single 12.5 mg dose of pyrimethamine. The weight adjusted cumulative RID was 30.2% (16.8–45.6%) [136]. Amount excreted in each day was not reported; RID for each day would presumably be < 10%. There are no data on sulfadoxine excretion in breast milk.

10. Chloroquine

Chloroquine is considered very safe in pregnancy and was used for treatment and prophylaxis (weekly dose) when *P. falciparum* was sensitive to the drug. It can still be used for the prophylaxis of *Plasmodium vivax* [137] and remains the first-line treatment for *P. vivax* infection in most endemic areas, although there are very few published studies on its use in pregnancy [17].

The risk/benefit ratio is excellent because adverse effects are rare and minor, and efficacy is high. In a cohort of US government employee taking chloroquine (300 mg weekly) as prophylaxis throughout pregnancy in 1969–1978, the prevalence of newborns with congenital abnormality (1.2%, 2/169) was not different from that of those who were not exposed to chloroquine (0.9%, 4/454) [138]. However, the drug would not be efficacious in a conventional IPTp regimen if given only 2–4 times during pregnancy. Combining chloroquine with azithromycin in an IPTp regimen is associated with more adverse effects (69% in the chloroquine-azithromycin group compared to 20% in the IPTp-SP group) and, as expected, was ineffective [139].

Chloroquine is the most widely studied antimalarial in breastfeeding, with several studies reporting pharmacokinetic data in lactating women [136,140–146]. Though actual pharmacokinetic parameters vary (due, in part, to methodologic differences), all studies yield a RID of < 10% when uniform calculations are applied to the data [142]. Though manufacturers recommend against its use during breastfeeding, exposure would be expected to be significantly lower than established therapeutic doses that are well-tolerated in neonates and infants.

The most recent study of chloroquine in lactation measured chloroquine and desethylchloroquine in 16 breastfeeding women. RID was low at 2.3% and the absolute infant dose was calculated to be 34 µg/kg/day, or 0.57 mg/kg cumulatively over the 17-day period following maternal treatment. No adverse events were seen in the exposed infants [142].

In addition to research and clinical experience with chloroquine for treatment of malaria, there is extensive research in the rheumatology literature on the effects on fetuses and breastfed infants of prolonged maternal treatment with hydroxychloroquine with reassuring results [147–149]. In summary, available data supports the compatibility of chloroquine treatment in pregnancy and with breastfeeding.

11. Primaquine and tafenoquine

Primaquine is an 8-aminoquinoline used in non-pregnant patients for radical cure of *vivax* and *ovale* infections, and as a gametocytocidal agent in *falciparum* malaria at a single low dose (0.25 mg/kg). Tafenoquine is an 8-aminoquinoline recently approved by FDA for the radical cure of *vivax* with a single-dose in non-pregnant patients.

Both primaquine and tafenoquine are contraindicated in pregnant women based on the theoretical risk of iatrogenic hemolysis in a G6PD-deficient fetus. Since G6PD deficiency cannot be readily ruled out in utero in the field, this contraindication is applied to all pregnant women, regardless of the prevalence of G6PD deficiency in the area.

There are no studies of primaquine or tafenoquine in pregnant women. Two preclinical studies in pregnant rats did not show fetotoxicity or embryotoxicity at high and prolonged dosages of primaquine [150,151], but neither tested models of G6PD deficient fetuses.

Studies of the risk of in-utero hemolysis with G6PD hemolytic agents yield mixed results. Some medications known to cause hemolysis are used routinely in pregnancy (for example nitrofurantoin and phenazopyridine), however primaquine is thought to be a more potent oxidizing agent than these other drugs. Case reports have been published of in-utero hemolysis, hydrops, or stillbirth associated with fetal G6PD deficiency and maternal ingestion of fava beans [152,153], sulfa-based antibiotics [154], and intravenous treatment with methylene blue [155]. However, a study prospectively measuring markers of subclinical hemolysis at birth in G6PD deficient neonates did not find a difference between those exposed to fava beans in-utero vs those not exposed [156]. The younger average age of erythrocytes in fetal and neonatal blood is theoretically protective against G6PD-mediated hemolysis, as evidenced by higher rates of false negative results on fluorescent spot tests for G6PD deficiency in the neonatal period, especially for preterm infants [157,158].

Overall, available data is insufficient to assuage fears of in-utero hemolysis. As primaquine use can normally be delayed until after the pregnancy is completed, current recommendations against its use in pregnancy remain. However, in the case of accidental exposure to primaquine, especially at the single low dose employed in treatment of falciparum malaria and in areas where G6PD deficiency is uncommon or mild, risk to the fetus can be considered low.

Current WHO guidelines caution against primaquine use in breastfeeding women during the first 6 months

postpartum, and at any time for women breastfeeding G6PD deficient infants and young children due to lack of data on breast milk excretion. Subsequently, one study of 21 G6PD normal lactating women breastfeeding G6PD normal infants 28 days and older found extremely low levels of primaquine the breastmilk correlating with a RID of 0.6% [159]. Total cumulative infant drug exposure over 14 days of treatment was estimated to be 0.042 mg/kg, and no adverse effects of the medication were seen. The authors conclude that, considering that primaquine-induced hemolysis is dose-dependent, these extremely low doses are very unlikely to cause harm, even in G6PD deficient infants [159]. Data are still needed in the first month of life to determine excretion in colostrum and transitional milk, though theoretical exposure during this period is low as breast milk volumes ingested by the infant in the first week of life are considerably smaller than those consumed later. Studies are needed to assess the safety of tafenoquine during breastfeeding.

12. Clindamycin

Clindamycin is used as a treatment (10 mg/kg/dose, three times a day for 7 days) in combination with either quinine or artesunate. Although clindamycin is not easily available in many malaria endemic countries, quinine should always be given together with clindamycin, to improve the low efficacy of quinine monotherapy [10].

Clindamycin is one of the few antibiotics that are generally regarded safe in pregnancy, including the first trimester [4,22,23]. Surveillance of Michigan Medicaid recipients between 1985 and 1992 reported that the prevalence of major congenital abnormality among those who were exposed to clindamycin during the first trimester was 4.8% (31/647) [23].

Data and recommendations on clindamycin use in lactating women are conflicting. The WHO's 2002 document on medications and breastfeeding recommends against its use, whereas the American Academy of Pediatrics considers clindamycin compatible with breastfeeding.

Small studies of 2–5 participants in the 1970s and '80s evaluated clindamycin excretion in breastmilk [160,161]. Observed maximum milk concentrations were trace to 3.8 µg/ml resulting in maximum potential doses to the infant of 570 µg/kg/day [162]. RID using mean concentrations was 1.6% [163]. An additional 1997 study of 15 patients reported mean breast milk values 2 hrs after 600 mg of clindamycin was administered intravenously were 1.03 µg/ml, confirming the reassuring results of the previous studies [164].

The cause for concern is a single case report in which an infant had grossly bloody stools while the mother was treated with clindamycin and gentamicin for endometritis [165]. The infant also directly received 48 h of antibiotics while sepsis was being ruled out. Symptoms resolved with temporary cessation of breastfeeding. Numerous potential alternate explanations of the hematochezia are apparent in this case, including perinatal infection, direct exposure to antibiotics, and maternal treatment with gentamicin.

Given the otherwise reassuring data, clindamycin should be considered a safe option for breastfeeding women. Monitoring for infant stool changes during maternal treatment is reasonable. Clindamycin's broad antimicrobial spectrum and potential impact on infant gut microbiome is a consideration that has not yet been studied.

13. Doxycycline

Doxycycline is an antibiotic with anti-malarial properties that is used for malaria prophylaxis and, in combination with quinine or artesunate, for treatment of uncomplicated malaria or follow-up treatment of severe malaria after intravenous medications are completed (100 mg twice a day given for seven days).

Doxycycline is contraindicated in pregnancy due to presumed shared toxic characteristics with tetracycline, primarily hepatotoxicity, permanent dental staining for exposed fetuses or children, and temporary slowing of bone growth all of which are more common with prolonged use. A recent comprehensive review summarizes the available evidence on doxycycline toxicity in pregnancy [166]. The adverse events seen with tetracycline are all either absent or significantly less common with doxycycline use compared with tetracycline. In addition, in-utero exposure to the tetracycline class causes staining of deciduous teeth only, limiting the potential long-term effects to offspring. Accidental exposure of pregnant women to doxycycline is unlikely to cause harm, and it is reasonable to consider doxycycline as an option where other preferred anti-malarials are unavailable [167].

Doxycycline use has been discouraged in lactating women for the same tetracycline class-effect concerns as pregnant women, particularly teeth staining in breastfed infants.

Several studies conducted in the 1960s and '70s evaluated the amount of doxycycline excreted in breast milk at 100 mg and 200 mg doses, and after single or repeated dosing [168–170] . One study found average peak concentrations of 0.96 mg/L after a single 100 mg dose (n = 3) and 1.8 mg/L after a single 200 mg dose (n = 3). After repeated twice daily 100 mg doses for 5 days, average breastmilk concentration increased to 3.6 mg/L [170]. Supporting this pattern of increasing excretion with repeated maternal doses, another study found doxycycline concentration to be 0.38 mg/L 24 h after a single 100 mg dose, and 0.46 mg/L after a second daily dose [168]. Other pharmacokinetic data are consistent with these studies [169]. RIDs based on these studies range from 4.2–13.3% [171]. Tetracycline has been rated as compatible with breastfeeding, partially because calcium binding of the drug in breastmilk limits its oral bioavailability to the nursing infant. Doxycycline in breast milk is less calcium bound than tetracycline, and therefore more bioavailable but less likely to affect teeth and bones [171].

Based on the available pharmacokinetic data, other options should be preferred as first-line antimalarials in breastfeeding women. However, it is likely that the risk to breastfeeding infants is low. As with clindamycin, impact of low doses of antibiotics on the infant gut microbiome may be a consideration.

14. Conclusion

Recent evidence shows that use of artemisinin derivatives and the first-line partner drugs in any trimester does not appear to be associated with increased risk of miscarriage, stillbirth or congenital abnormality compared to those who are treated with quinine or to the background population level in women who do not need antimalarial treatment. ACTs also offer better efficacy and tolerability. Clindamycin, atovaquone-proguanil and doxycycline are also likely safe in pregnancy and can be options as partner drugs of artemisinins particularly when other options are not available, but further evaluation is needed. Dose optimization for pregnant women is warranted and monitoring of fetal safety should be continued alongside the implementation of ACTs in pregnancy.

First-line ACTs, particularly DP, also appear safe in lactating mothers and their breastfed infants. Well-designed toxicokinetic studies are still required in this pregnancy and lactation. In the current era of malaria elimination in many parts of the world, primaquine should be considered in breastfeeding women.

New approaches alongside vector control are needed for prevention of malaria in pregnancy facing the widespread resistance to SP and increasing failure of the current policy.

15. Expert opinion

Malaria in pregnancy can result in severe and fatal outcomes for both mother and fetus, or to more covert adverse effects such as being born small for gestational age with lifelong implications. Safe, efficacious and affordable antimalarials with assured quality are needed for treating and preventing malaria in pregnancy. Therapeutics in lactating women remains a neglected area, and lack of data leads healthcare workers to advise cessation of breastfeeding or use of non-preferred medications with potentially serious consequences. In both situations, toxicity of antimalarial drugs and potential acquired clinical benefits need to be balanced. The safety of a drug is usually dose dependent and relates to the frequency of administration. In pregnancy and lactation, the safety assessment is further complicated by potential impacts on the unborn or breastfed child, and the altered pharmacokinetics in pregnancy and lactation. The variability of safety assessment and reporting in studies of antimalarials in pregnancy and also of breastfeeding make it difficult to draw a summary conclusion with high evidence grade [172].

Quinine has been recommended for the first trimester women, despite the limited evidence on efficacy and safety at treatment dose [83], and possible teratogenicity at overdose [23]. Over the last decade, evidence on the safety of artemisinin derivatives in pregnancy including the first trimester has been gathered, debunking fears based on animal studies that lead to the systematic use of antiquated antimalarials for pregnant women. Use of artemisinin derivatives in any trimester does not appear to be associated with increased risk of miscarriage, stillbirth or congenital abnormality compared to those who are treated with quinine or to the background population level [5,6,32]. Artemisinin-based therapy is more efficacious and is well-tolerated in pregnancy [10]. Given the benefits to both mother and fetus of effective maternal treatment, ACTs (e.g. DP, AL, ASMQ, ASAQ) should be considered first-line for treating all pregnant and lactating women with uncomplicated falciparum malaria (Table 1). Ongoing systematic monitoring for adverse effects should be strengthened and continued.

Because of the altered immunity and pharmacokinetics in pregnancy in addition to the sequestration of parasites to placenta, simple extrapolation of the efficacy results from non-pregnant population may not be necessarily valid. Although it has the safest profile among ACTs, the efficacy of AL can be lower possibly because of the suboptimal dosing for pregnant women. Dose optimization, usually by increasing the dosage, can be required for some antimalarials in pregnancy, and these alternate regimens require further evaluation of treatment efficacy and safety in pregnant women and their offspring. Clindamycin, doxycycline and atovaquone-proguanil are considered safe in pregnancy and can be options as partner drugs with artemisinins, although these combinations of short half-life drugs will lead to shorter post-treatment prophylaxis. Newer drugs, such as pyronaridine or naphthoquine require investigation of reproductive toxicity without delay. In the setting of malaria elimination, drug efficacy can be attenuated because of declining immunity, and this can theoretically be exacerbated by the relative immune suppression during pregnancy, resulting in the urgent need for antimalarials in the development pathway that are efficacious and safe in pregnancy.

For the prevention of malaria in pregnant women, there are two approaches using antimalarial medicines: prophylaxis and IPTp. The former implies the frequent administration of a prophylactic (low) dose at regular intervals while the later involves the administration of a curative (higher) dose, less frequently during pregnancy. The distinction is important because these medicines are given to presumably healthy subjects, and their safety is dependent on the risk/benefit ratio.

If the objective is to prevent malaria in the mother, the primary benefit should be the absence of parasites in her blood and placenta during gestation and at delivery. However, this is generally not the case and in numerous studies, the benefit is measured by using proxies such as birth outcomes (usually the birthweight), rather than the absence of malaria parasites in the mother. In addition, the recommended doses of antimalarials used for IPTp (related to their safety) are often not based on the pharmacokinetic and pharmacodynamic properties of the drug [174]. As a consequence, they are often inadequate to achieve the main objective: a circulating concentration of the drug that will prevent malaria parasites replication, resulting in an unfavorable risk/benefit ratio. More than a decade ago, an editorial noted that *'It is remarkable that, after a decade of policy recommendations, we are still seeking information on optimal dosing frequency for IPTp'* [175]. Very little progress has been made since this statement was published. Finally, there is no strategy to prevent malaria in the first trimester of pregnancy, despite evidence of the deleterious effects of the disease on the mother and the fetus.

Table 1. Summary of antimalarial drugs for treating uncomplicated falciparum and vivax malaria in pregnant and lactating women with levels of evidence.

Drug	Efficacy	Maternal adverse reaction	Effect on fetus	Breastfeeding	Comment
Treatment for uncomplicated falciparum malaria in pregnancy					
Quinine	– Lower efficacy than ACTs (RR of treatment failure 4.67, 95% CI 1.60 - 13.67) [10] (High)	– Higher risk of adverse reactions compared to ACT: cinchonism (tinnitus, nausea, vomiting, dizziness, anorexia) and hypoglycemia (High)	– 947 women exposed in the first trimester [5]: higher risk of miscarriage (aHR 1.48, 95% CI 1.18–1.86, p = 0.001)*; similar risk of stillbirth (aHR 1.35, 95% CI 0.69–2.65, p = 0.39)*; similar congenital abnormality (1.2%, 95% CI 0.6–2.4%) (Moderate)	– Excreted in breast milk, only one study [34] – Theoretical risk of hypersensitivity reaction (Low)	– Increased dose may be needed (Low) – Supervision is needed as adherence is low (High) – Quinine+ clindamycin can be an option if ACT cannot be used (Moderate)
ACT	– Higher efficacy than quinine – Faster parasite clearance – Lower risk of gametocyte carriage (High)	– Well-tolerated in pregnancy – Allergy to artemisinins is rare (1 in 2833) [46] (High)	– 717 women exposed in the first trimester [5]: possibly lower risk of miscarriage (aHR 0.73, 95% CI 0.44–1.21, p = 0.23)‡; possibly lower risk of stillbirth (aHR 0.29, 95% CI 0.08–1.02, p = 0.053)‡; similar congenital abnormality (1.5%, 95%CI 0.6–3.5%) (Moderate) – In the 2nd and 3rd trimesters: similar to quinine and no apparent difference among different ACTs (Moderate)	– Dihydroartemis-inin is excreted in breast milk at very low level (Low)	– Increased artemisinin doses may be needed (Moderate) – Artemisinin monotherapy is discouraged (High)
AL	– Possibly lower efficacy than other ACTs at the current dosage (Low)	– Well-tolerated than other ACTs (High)	– AL has the largest number of documented fetal safety among ACTs including > 500 women in the first trimester (High)	– Excreted in breast milk at borderline levels in rats. No human data (Very Low)	– Dose adjustment should be considered for pregnant women (High)
ASAQ	– Efficacy > 95% in Africa, but no data in Asia (Moderate)	– More anorexia, nausea, vomiting, dizziness and weakness than AL – Hypotension (1.5%) [69] (High)	– Limited evidence in the first trimester but considered safe based on the structural similarity to CHQ (Moderate)	– More data needed, avoid if possible (Very Low)	– Limited PK data suggest no changes in pregnancy (Low)
ASMQ	– Efficacy > 95% in Africa and Asia (High)	– More adverse reactions (anorexia, nausea, vomiting and dizziness) than AL but better than quinine – Early vomiting is common – Uncommon symptoms include behavioral change and insomnia (High)	– No increased risk in any trimesters (Moderate)	– Excreted in breast milk at low level (Moderate)	– PK data are not consistent (Low) – Long-term neurocognitive development in exposed fetuses/neonates needs to be assessed (Moderate)
DP	– Efficacy > 95% in Africa and Asia (High)	– Well-tolerated: less adverse reactions than ASAQ or ASMQ (High)	– Limited evidence in the first trimester but no reproductive toxicity was reported in animals (Moderate)	– Excreted in breast milk at very low level, one recent study [117]. Best option for ACT in lactation (Moderate)	– PK data are not consistent (Low)
AAP	– Efficacy > 95% mostly from Asia (Moderate)	– Well-tolerated (High)	– No increased risks after the exposure of AP in the first trimester (n > 300) (Moderate)	– Proguanil is excreted in breast milk, rat data only for atovaquone (Very low)	– Increased dose may be needed (Moderate) – Co-administration of folic acid should be considered in the first trimester (Low)
Treatment for uncomplicated vivax malaria in pregnancy					
CHQ	– First-line treatment for vivax malaria with limited literature in pregnancy (High)	– Well-tolerated – Pruritus is common in Africa – Impaired vision after long-term use (High)	– The most accumulated evidence on safety in pregnancy in all trimesters (High)	– Excreted in breast milk at low level: compatible with breastfeeding (High)	– Reassuring safety evidence extensively from both malariology and rheumatology literature (High)

AAP: artesunate-atovaquone-proguanil. ACT: artemisinin-based combination therapy. AL: artemether-lumefantrine. AP: atovaquone-proguanil. ASAQ: artesunate-amodiaquine. ASMQ: artesunate-mefloquine. CHQ: chloroquine. DP: dihydroartemisinin-piperaquine. HR: hazard ratio. PK: pharmacokinetic. RR: risk ratio. 95%CI: 95% confidence interval.

* Compared to pregnant women who were not exposed to any antimalarials in the first trimester. ‡: Compared to pregnant women who were treated with quinine in the first trimester.

The level of evidence shown in round brackets is adopted from the GRADE scale [173]: Very low (The true effect is probably markedly different from the estimated effect); Low (The true effect might be markedly different from the estimated effect); Moderate (The authors believe that the true effect is probably close to the estimated effect); High (The authors have a lot of confidence that the true effect is similar to the estimated effect).

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References

1. Desai M, Ter Kuile FO, Nosten F, et al. Epidemiology and burden of malaria in pregnancy. Lancet Infect Dis. 2007;7(2):93–104.
2. Gomes C, Boareto AC, Dalsenter PR. Clinical and non-clinical safety of artemisinin derivatives in pregnancy. Reprod Toxicol. 2016;65:194–203.
3. Clark RL. Embryotoxicity of the artemisinin antimalarials and potential consequences for use in women in the first trimester. Reprod Toxicol. 2009;28(3):285–296.
4. WHO. Guidelines for the treatment of malaria. Third ed. Geneva: World Health Organization; 2015.
5. Dellicour S, Sevene E, McGready R, et al. First-trimester artemisinin derivatives and quinine treatments and the risk of adverse pregnancy outcomes in Africa and Asia: A meta-analysis of observational studies. PLoS Med. 2017;14(5):e1002290.
•• **Collaborative work showing the safety of artemisinin derivatives in the first trimester by combining individual patient data of 6,666 pregnancies in six African sites and aggregated data of 23,952 pregnancies on the Thailand-Myanmar border.**
6. Moore KA, Simpson JA, Paw MK, et al. Safety of artemisinins in first trimester of prospectively followed pregnancies: an observational study. Lancet Infect Dis. 2016;16(5):576–583.
7. Nosten F, Ter Kuile F, Kl T, et al. Spiramycin does not potentiate quinine treatment of falciparum malaria in pregnancy. Trans R Soc Trop Med Hyg. 1993;87(3):305–306.
8. Kloprogge F, Jullien V, Piola P, et al. Population pharmacokinetics of quinine in pregnant women with uncomplicated Plasmodium falciparum malaria in Uganda. J Antimicrob Chemother. 2014;69(11):3033–3040.
9. Tarning J, Kloprogge F, Dhorda M, et al. Pharmacokinetic properties of artemether, dihydroartemisinin, lumefantrine, and quinine in pregnant women with uncomplicated Plasmodium falciparum malaria in Uganda. Antimicrob Agents Chemother. 2013;57(10):5096–5103.
10. Saito M, Gilder ME, Nosten F, et al. Systematic literature review and meta-analysis of the efficacy of artemisinin-based and quinine-based treatments for uncomplicated falciparum malaria in pregnancy: methodological challenges. Malar J. 2017;16:488.
11. 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(5):846–853.
12. 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(11):762–769.
13. McGready R, Cho T, Samuel VL, et al. Randomized comparison of quinine-clindamycin versus artesunate in the treatment of falciparum malaria in pregnancy. Trans R Soc Trop Med Hyg. 2001;95(6):651–656.
14. Bounyasong S. Randomized trial of artesunate and mefloquine in comparison with quinine sulfate to treat P. falciparum malaria pregnant women. J Med Assoc Thai. 2001;84(9):1289–1299.
15. McGready R, Brockman A, Cho T, et al. Randomized comparison of mefloquine-artesunate versus quinine in the treatment of multidrug-resistant falciparum malaria in pregnancy. Trans R Soc Trop Med Hyg. 2000;94(6):689–693.
16. Taylor WR, White NJ. Antimalarial drug toxicity: a review. Drug Saf. 2004;27(1):25–61.
17. McGready R, Thwai KL, Cho T, et al. The effects of quinine and chloroquine antimalarial treatments in the first trimester of pregnancy. Trans R Soc Trop Med Hyg. 2002;96(2):180–184.
18. Adam I, Ibrahim MH, Ia A, et al. Low-dose quinine for treatment of chloroquine-resistant falciparum malaria in Sudanese pregnant women. East Mediterr Health J. 2004;10(4/5):554–559.
19. McGready R, Nosten F. The Thai-Burmese border: drug studies of Plasmodium falciparum in pregnancy. Ann Trop Med Parasitol. 1999;93(Suppl 1):S19–23.
20. Looareesuwan S, Phillips RE, White NJ, et al. Quinine and severe falciparum malaria in late pregnancy. Lancet. 1985;2(8445):4–8.
21. White NJ, Warrell DA, Chanthavanich P, et al. Severe hypoglycemia and hyperinsulinemia in falciparum malaria. N Engl J Med. 1983;309(2):61–66.
22. Clark RL. Animal embryotoxicity studies of key non-artemisinin antimalarials and use in women in the first trimester. Birth Defects Res. 2017;109(14):1075–1126.
23. Briggs GG, Freeman RK, Towers CV, et al. ed. Drugs in Pregnancy and Lactation. 11th. Philadelphia, Pennsylvania, US: Wolters Kluwer Health; 2016.
24. Dellicour S, Desai M, Aol G, et al. Risks of miscarriage and inadvertent exposure to artemisinin derivatives in the first trimester of pregnancy: a prospective cohort study in western Kenya. Malar J. 2015;14:461.
25. Manyando C, Mkandawire R, Puma L, et al. Safety of artemether-lumefantrine in pregnant women with malaria: results of a prospective cohort study in Zambia. Malar J. 2010;9:249.
26. Mosha D, Mazuguni F, Mrema S, et al. Safety of artemether-lumefantrine exposure in first trimester of pregnancy: an observational cohort. Malar J. 2014;13:197.
27. Rulisa S, Kaligirwa N, Agaba S, et al. Pharmacovigilance of artemether-lumefantrine in pregnant women followed until delivery in Rwanda. Malar J. 2012;11:225.
28. Tinto H, Sevene E, Dellicour S, et al. Assessment of the safety of antimalarial drug use during early pregnancy (ASAP): protocol for a multicenter prospective cohort study in Burkina Faso, Kenya and Mozambique. Reprod Health. 2015;12:112.
29. Manyando C, Njunju EM, Virtanen M, et al. Exposure to artemether-lumefantrine (Coartem) in first trimester pregnancy in an observational study in Zambia. Malar J. 2015;14:77.
30. Poespoprodjo JR, Fobia W, Kenangalem E, et al. Dihydroartemisinin-piperaquine treatment of multidrug resistant falciparum and vivax malaria in pregnancy. PLoS One. 2014;9(1):e84976.
31. Adam I, Idris HM, Elbashir MI. Quinine for chloroquine-resistant falciparum malaria in pregnant Sudanese women in the first trimester. East Mediterr Health J. 2004;10(4/5):560–565.
32. Kovacs SD, van Eijk AM, Sevene E, et al. The safety of artemisinin derivatives for the treatment of malaria in the 2nd or 3rd trimester of pregnancy: A systematic review and meta-analysis. PLoS One. 2016;11(11):e0164963.

33. Terwilliger WG, Hatcher RA. The elimination of morphine and quinine in human milk. Surg Gynecol Obstet. 1934;58:823–826.
34. Phillips RE, Looareesuwan S, White NJ, et al. Quinine pharmacokinetics and toxicity in pregnant and lactating women with falciparum malaria. Br J Clin Pharmacol. 1986;21(6):677–683.
35. Bichali S, Brault D, Masserot C, et al. Maternal consumption of quinine-containing sodas may induce G6PD crises in breastfed children. Eur J Pediatr. 2017;176(10):1415–1418.
36. Youngster I, Arcavi L, Schechmaster R, et al. Medications and glucose-6-phosphate dehydrogenase deficiency: an evidence-based review. Drug Saf. 2010;33(9):713–726.
37. McGready R, Stepniewska K, Lindegardh N, et al. The pharmacokinetics of artemether and lumefantrine in pregnant women with uncomplicated falciparum malaria. Eur J Clin Pharmacol. 2006;62 (12):1021–1031.
38. McGready R, Stepniewska K, Ward SA, et al. Pharmacokinetics of dihydroartemisinin following oral artesunate treatment of pregnant women with acute uncomplicated falciparum malaria. Eur J Clin Pharmacol. 2006;62(5):367–371.
39. Kloprogge F, McGready R, Phyo AP, et al. Opposite malaria and pregnancy effect on oral bioavailability of artesunate - a population pharmacokinetic evaluation. Br J Clin Pharmacol. 2015;80(4):642–653.
40. McGready R, Phyo AP, Rijken MJ, et al. Artesunate/dihydroartemisinin pharmacokinetics in acute falciparum malaria in pregnancy: absorption, bioavailability, disposition and disease effects. Br J Clin Pharmacol. 2012;73(3):467–477.
41. Morris CA, Onyamboko MA, Capparelli E, et al. Population pharmacokinetics of artesunate and dihydroartemisinin in pregnant and non-pregnant women with malaria. Malar J. 2011;10:114.
42. Onyamboko MA, Meshnick SR, Fleckenstein L, et al. Pharmacokinetics and pharmacodynamics of artesunate and dihydroartemisinin following oral treatment in pregnant women with asymptomatic Plasmodium falciparum infections in Kinshasa DRC. Malar J. 2011;10:49.
43. Rijken MJ, McGready R, Phyo AP, et al. Pharmacokinetics of dihydroartemisinin and piperaquine in pregnant and nonpregnant women with uncomplicated falciparum malaria. Antimicrob Agents Chemother. 2011;55(12):5500–5506.
44. Tarning J, Mj R, McGready R, et al. Population pharmacokinetics of dihydroartemisinin and piperaquine in pregnant and nonpregnant women with uncomplicated malaria. Antimicrob Agents Chemother. 2012;56(4):1997–2007.
45. Rehman K, Lötsch F, Kremsner PG, et al. Haemolysis associated with the treatment of malaria with artemisinin derivatives: a systematic review of current evidence. Int J Infect Dis. 2014;29:268–273.
46. Leonardi E, Gilvary G, White NJ, et al. Severe allergic reactions to oral artesunate: a report of two cases. Trans R Soc Trop Med Hyg. 2001;95(2):182–183.
47. 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 (12):2009–2016.
48. McGready R, Tan SO, Ashley EA, et al. A randomised controlled trial of artemether-lumefantrine versus artesunate for uncomplicated Plasmodium falciparum treatment in pregnancy. PLoS Med. 2008;5(12):e253.
49. Adam I, Elhassan EM, Omer EM, et al. Safety of artemisinins during early pregnancy, assessed in 62 Sudanese women. Ann Trop Med Parasitol. 2009;103(3):205–210.
50. Adam I, Elwasila E, Mohammed Ali DA, et al. Artemether in the treatment of falciparum malaria during pregnancy in eastern Sudan. Trans R Soc Trop Med Hyg. 2004;98(9):509–513.
51. Deen JL, von Seidlein L, Pinder M, et al. The safety of the combination artesunate and pyrimethamine-sulfadoxine given during pregnancy. Trans R Soc Trop Med Hyg. 2001;95(4):424–428.
52. Willcox ML, Burton S, Oyweka R, et al. Evaluation and pharmacovigilance of projects promoting cultivation and local use of Artemisia annua for malaria. Malar J. 2011;10:84.
53. Rouamba T, Kpoda H, Valea I, et al. Safety of antimalarial drug use during early pregnancy in Bobo Dioulasso: examining low birth weight and congenital malformations as potential adverse outcomes. Trop Med Int Health. Conference:10th European Congress on Tropical Medicine and International Health. Belgium. 2017;22 (Supplement 1):95.
54. Manirakiza A, Soula G, Laganier R, et al. Pattern of the antimalarials prescription during pregnancy in Bangui, Central African Republic. Malar Res Treat. 2011;2011:414510.
55. Sangaré LR, Weiss NS, Brentlinger PE, et al. Patterns of anti-malarial drug treatment among pregnant women in Uganda. Malar J. 2011;10:152.
56. Jansen F, Jansen-Luts A, Ameye C, et al. Is artesunate or its active metabolite dihydroartemisinin being excreted in the milk of lactating mothers? Am J Trop Med Hyg. 2006;75:(5-Suppl):158.
57. Ballard SB, Salinger A, Mphc APM, et al. Updated CDC Recommendations for Using Artemether-Lumefantrine for the Treatment of Uncomplicated Malaria in Pregnant Women in the United States. MMWR Morb Mortal Wkly Rep. 2018;67(14):424–431.
58. Kloprogge F, McGready R, Hanpithakpong W, et al. Lumefantrine and desbutyl-lumefantrine population pharmacokinetic-pharmacodynamic relationships in pregnant women with uncomplicated Plasmodium falciparum malaria on the Thailand-Myanmar border. Antimicrob Agents Chemother. 2015;59(10):6375–6384.
59. Kloprogge F, Piola P, Dhorda M, et al. Population pharmacokinetics of lumefantrine in pregnant and nonpregnant women with uncomplicated Plasmodium falciparum malaria in Uganda. CPT Pharmacometrics Syst Pharmacol. 2013;2:11.
60. Tarning J, McGready R, Lindegardh N, et al. Population pharmacokinetics of lumefantrine in pregnant women treated with artemether-lumefantrine for uncomplicated Plasmodium falciparum malaria. Antimicrob Agents Chemother. 2009;53(9):3837–3846.
61. Mutagonda RF, Kamuhabwa AA, Minzi OM, et al. Malaria prevalence, severity and treatment outcome in relation to day 7 lumefantrine plasma concentration in pregnant women. Malar J. 2016;15:278.
62. Mutagonda RF, Kamuhabwa AAR, Minzi OMS, et al. Effect of pharmacogenetics on plasma lumefantrine pharmacokinetics and malaria treatment outcome in pregnant women. Malar J. 2017;16:267.
63. Mosha D, Guidi M, Mwingira F, et al. Population pharmacokinetics and clinical response for artemether-lumefantrine in pregnant and nonpregnant women with uncomplicated Plasmodium falciparum malaria in Tanzania. Antimicrob Agents Chemother. 2014;58 (8):4583–4592.
64. Nyunt MM, Nguyen VK, Kajubi R, et al. Artemether-lumefantrine pharmacokinetics and clinical response are minimally altered in pregnant Ugandan women treated for uncomplicated falciparum malaria. Antimicrob Agents Chemother. 2016;60(3):1274–1282.
65. Kloprogge F, Workman L, Borrmann S, et al. Artemether-lumefantrine dosing for malaria treatment in young children and pregnant women: A pharmacokinetic-pharmacodynamic meta-analysis. PLoS Med. 2018;15(6):e1002579.
66. Onyamboko MA, Fanello CI, Turner G, et al. Comparison of two regimens of artemetherlumefantrine for the treatment of uncomplicated Plasmodium falciparum malaria in pregnant women in the democratic republic of Congo. Am J Trop Med Hyg. Conference:64th Annual Meeting of the American Society of Tropical Medicine and Hygiene, ASTMH 2015. United States. 2015;93(4 Supplement):5.
67. McGready R. Randomised Trial of 3 Artemisinin Combination Therapy for Malaria in Pregnancy (NCT01054248). 2010 [cited 2018 Jul 16]; Available from: https://clinicaltrials.gov/ct2/show/NCT01054248
68. Jain JP, Leong FJ, Chen L, et al. Bioavailability of lumefantrine is significantly enhanced with a novel formulation approach, an outcome from a randomized, open-label pharmacokinetic study in healthy volunteers. Antimicrob Agents Chemother. 2017;61(9): e00868-17.

69. PREGACT Study Group. Four artemisinin-based treatments in African pregnant women with malaria. N Engl J Med. 2016;374(10):913–927.
    - **A large-scale multi-centrer RCT in four sub-Saharan African countries comparing AL, ASAQ, ASMQ and DP in pregnancy.**
70. Iribhogbe OI, Emmanuel I, Odianosen M. Comparative analysis of the safety and tolerability of fixed-dose artesunate/amodiaquine versus artemether/lumefantrine combinations for uncomplicated falciparum malaria in pregnancy: a randomized open label study. Clin Pharmacol. 2017;9:45–54.
71. Kaye DK, Nshemerirwe R, Mutyaba TS, et al. 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(2):135–139.
72. Jain JP, Ganesan S, Lefevre G, et al. Estimating of the amount of artemether and lumefantrine excreted through breast milk. Trop Med Int Health. 2015;20(Suppl.S1):184–185.
73. Rijken MJ, McGready R, Jullien V, et al. Pharmacokinetics of amodiaquine and desethylamodiaquine in pregnant and postpartum women with Plasmodium vivax malaria. Antimicrob Agents Chemother. 2011;55(9):4338–4342.
74. Tarning J, Chotsiri P, Jullien V, et al. Population pharmacokinetic and pharmacodynamic modeling of amodiaquine and desethylamodiaquine in women with Plasmodium vivax malaria during and after pregnancy. Antimicrob Agents Chemother. 2012;56(11):5764–5773.
75. Mutabingwa TK, Muze K, Ord R, et al. Randomized trial of artesunate+amodiaquine, sulfadoxine-pyrimethamine+amodiaquine, chlorproguanal-dapsone and SP for malaria in pregnancy in Tanzania. PLoS One. 2009;4(4):e5138.
76. Ndiaye JL, Ndiaye A, Faye B, et al. Open-label in vivo drug study to evaluate the safety and efficacy of artesunate plus amodiaquine combination in pregnant women with uncomplicated P falciparum malaria in Senegal. Trop Med Int Health. 2011;16(Supplement 1):140.
77. Moore BR, Salman S, Davis TM. Treatment regimens for pregnant women with falciparum malaria. Expert Rev Anti Infect Ther. 2016;14(8):691–704.
78. Ukah M, Badejoko O, Ogunniyi S, et al. A randomized trial of artesunate-amodiaquine versus artemether-lumefantrine for the treatment of acute uncomplicated malaria in pregnancy. Int J Gynaecol Obstet. 2015;131(1):41–44.
79. Osarfo J, Tagbor H, Cairns M, et al. Dihydroartemisinin-piperaquine versus artesunate-amodiaquine for treatment of malaria infection in pregnancy in Ghana: an open-label, randomised, non-inferiority trial. Trop Med Int Health. 2017;22(8):1043–1052.
80. Tagbor H, Bruce J, Browne E, et al. Efficacy, safety, and tolerability of amodiaquine plus sulphadoxine-pyrimethamine used alone or in combination for malaria treatment in pregnancy: a randomised trial. Lancet. 2006;368(9544):1349–1356.
81. Clerk CA, Bruce J, Affipunguh PK, et al. A randomized, controlled trial of intermittent preventive treatment with sulfadoxine-pyrimethamine, amodiaquine, or the combination in pregnant women in Ghana. J Infect Dis. 2008;198(8):1202–1211.
82. Iribhogbe OI, Igue EO, Odianosen M. Assessment of the safety of non-fixed-dose combination of artesunate and amodiaquine for uncomplicated falciparum malaria in pregnancy: a nonrandomized open-label study. J Pharm Health Serv Res. 2017;8(1):31–38.
83. Nosten F, McGready R, d'Alessandro U, et al. Antimalarial drugs in pregnancy: a review. Curr Drug Saf. 2006;1(1):1–15.
84. Burger RJ, Visser BJ, Grobusch MP, et al. The influence of pregnancy on the pharmacokinetic properties of artemisinin combination therapy (ACT): a systematic review. Malar J. 2016;15:99.
85. Nosten F, Karbwang J, White NJ, et al. Mefloquine antimalarial prophylaxis in pregnancy: dose finding and pharmacokinetic study. Br J Clin Pharmacol. 1990;30(1):79–85.
86. Na Bangchang K, Davis TME, Looareesuwan S, et al. Mefloquine pharmacokinetics in pregnant women with acute falciparum malaria. Trans R Soc Trop Med Hyg. 1994;88(3):321–323.
87. Valea I, Tinto H, Traore-Coulibaly M, et al. Pharmacokinetics of co-formulated mefloquine and artesunate in pregnant and non-pregnant women with uncomplicated Plasmodium falciparum infection in Burkina Faso. J Antimicrob Chemother. 2014;69(9):2499–2507.
88. Carmona-Fonseca J, Agudelo-García OM, Arango-Flórez E. [Therapeutic efficacy and adverse events of treatments for vivax and falciparum malaria in pregnant women in the regions of Uraba and Alto San Jorge, Colombia, 2008–2011] (in Spanish). Rev Colomb Obstet Ginecol. 2013;64(1):27–37.
89. Sowunmi A, Oduola AM, Ogundahunsi OA, et al. Randomised trial of artemether versus artemether and mefloquine for the treatment of chloroquine/sufadoxine-pyrimethamine-resistant falciparum malaria during pregnancy. J Obstet Gynaecol. 1998;18(4):322–327.
90. Anvikar AR, Kuepfer I, Mishra V, et al. Efficacy of two artemisinin-based combinations for the treatment of malaria in pregnancy in India: a randomized controlled trial. Malar J. 2018;17:246.
91. McGready R, Cho T, Hkirijaroen L, et al. Quinine and mefloquine in the treatment of multidrug-resistant Plasmodium falciparum malaria in pregnancy. Ann Trop Med Parasitol. 1998;92(6):643–653.
92. Adam I, Da A, Alwaseila A, et al. Mefloquine in the treatment of falciparum malaria during pregnancy in Eastern Sudan. Saudi Med J. 2004;25(10):1400–1402.
93. Nosten F, Ter Kuile F, Maelankiri L, et al. Mefloquine prophylaxis prevents malaria during pregnancy: a double-blind, placebo-controlled study. J Infect Dis. 1994;169(3):595–603.
94. Smoak BL, Writer JV, Keep LW, et al. The effects of inadvertent exposure of mefloquine chemoprophylaxis on pregnancy outcomes and infants of US Army servicewomen. J Infect Dis. 1997;176(3):831–833.
95. Phillips-Howard PA, Steffen R, Kerr L, et al. Safety of mefloquine and other antimalarial agents in the first trimester of pregnancy. J Travel Med. 1998;5(3):121–126.
96. Schlagenhauf P, Blumentals WA, Suter P, et al. Pregnancy and fetal outcomes after exposure to mefloquine in the pre- and periconception period and during pregnancy. Clin Infect Dis. 2012;54(11):e124–31.
97. Vanhauwere B, Maradit H, Kerr L. Post-marketing surveillance of prophylactic mefloquine (Lariam) use in pregnancy. Am J Trop Med Hyg. 1998;58(1):17–21.
98. Harinasuta T, Kietinun S, Sb S, et al. A clinical trial of mefloquine on multi-resistant falciparum malaria in pregnant women in Thailand. Bulletin De La Societe Francaise De Parasitologie. 1990;*419*:419.
99. Sowunmi A, Ilesanmi AO, Amj O, et al. Efficacy of mefloquine in uncomplicated chloroquine-resistant falciparum malaria during pregnancy. J Obstet Gynaecol. 1996;16(5):362–363.
100. Morof DF, Carroll ID. Advising travelers with specific needs: pregnant travelers. In: Centers for Disease Control and Prevention, ed. CDC yellow book 2018: health information for international travel. New York, NY: Oxford University Press; 2017:576–581.
101. González R, Pons-Duran C, Piqueras M, et al. Mefloquine for preventing malaria in pregnant women. Cochrane Database Syst Rev. 2018;3(3):CD011444.
102. Lee SJ, Ter Kuile FO, Rn P, et al. Adverse effects of mefloquine for the treatment of uncomplicated malaria in Thailand: A pooled analysis of 19, 850 individual patients. PLoS One. 2017;12(2):e0168780.
103. Gonzalez R, Desai M, Macete E, et al. Intermittent preventive treatment of malaria in pregnancy with mefloquine in HIV-infected women receiving cotrimoxazole prophylaxis: a multicenter randomized placebo-controlled trial. PLoS Med. 2014;11(9):e1001735.
104. Edstein MD, Veenendaal JR, Hyslop R. Excretion of mefloquine in human breast milk. Chemo. 1988;34(3):165–169.
105. Schlagenhauf P, Adamcova M, Regep L, et al. Use of mefloquine in children - a review of dosage, pharmacokinetics and tolerability data. Malar J. 2011;10:292.
106. Rm H, Adam I, Hanpithakpong W, et al. A population pharmacokinetic model of piperaquine in pregnant and non-pregnant women with uncomplicated Plasmodium falciparum malaria in Sudan. Malar J. 2012;11:398.
107. Adam I, Tarning J, Lindegardh N, et al. Pharmacokinetics of piperaquine in pregnant women in Sudan with uncomplicated

Plasmodium falciparum malaria. Am J Trop Med Hyg. 2012;87 (1):35–40.
108. Benjamin JM, Moore BR, Salman S, et al. Population pharmacokinetics, tolerability, and safety of dihydroartemisinin-piperaquine and sulfadoxine-pyrimethamine-piperaquine in pregnant and non-pregnant Papua New Guinean women. Antimicrob Agents Chemother. 2015;59(7):4260–4271.
109. Rijken MJ, McGready R, Boel ME, et al. Dihydroartemisinin-piperaquine rescue treatment of multidrug-resistant Plasmodium falciparum malaria in pregnancy: a preliminary report. Am J Trop Med Hyg. 2008;78(4):543–545.
110. Desai M, Gutman J, L'Lanziva A, et al. Intermittent screening and treatment or intermittent preventive treatment with dihydroartemisinin-piperaquine versus intermittent preventive treatment with sulfadoxine-pyrimethamine for the control of malaria during pregnancy in western Kenya: an open-label, three-group, randomised controlled superiority trial. Lancet. 2015;386(10012):2507–2519.
111. Kajubi R, Huang L, Jagannathan P, et al. Antiretroviral therapy with efavirenz accentuates pregnancy-associated reduction of dihydroartemisinin-piperaquine exposure during malaria chemoprevention. Clin Pharmacol Ther. 2017;102(3):520–528.
112. Kakuru A, Jagannathan P, Muhindo MK, et al. Dihydroartemisinin–piperaquine for the prevention of malaria in pregnancy. N Engl J Med. 2016;374(10):928–939.
113. Wallender E, Vucicevic K, Jagannathan P, et al. Predicting optimal dihydroartemisinin-piperaquine regimens to prevent malaria during pregnancy for human immunodeficiency virus-infected women receiving efavirenz. J Infect Dis. 2018;217(6):964–972.
114. Batty KT, Moore BR, Stirling V, et al. Investigation of reproductive toxicity of piperaquine in mice. Reprod Toxicol. 2010;29(2):206–213.
115. Lwin KM, Phyo AP, Tarning J, et al. Randomized, double-blind, placebo-controlled trial of monthly versus bimonthly dihydroartemisinin-piperaquine chemoprevention in adults at high risk of malaria. Antimicrob Agents Chemother. 2012;56(3):1571–1577.
116. Permala J, Tarning J, Nosten F, et al. Prediction of improved antimalarial chemoprevention with weekly dosing of dihydroartemisinin-piperaquine. Antimicrob Agents Chemother. 2017;61(5): e02491-16.
117. Moore BR, Salman S, Benjamin J, et al. Pharmacokinetics of piperaquine transfer into the breast milk of Melanesian mothers. Antimicrob Agents Chemother. 2015;59(7):4272–4278.
118. McGready R, Ashley E, Nosten F, et al. The prevention of malaria in pregnancy [royal college of obstetricians and gynaecologists green-top guideline no. 54a]. London, UK: Royal College of Obstetricians and Gynaecologists; 2010.
119. McGready R, Stepniewska K, Edstein MD, et al. The pharmacokinetics of atovaquone and proguanil in pregnant women with acute falciparum malaria. Eur J Clin Pharmacol. 2003;59(7):545–552.
120. Na-Bangchang K, Manyando C, Ruengweerayut R, et al. The pharmacokinetics and pharmacodynamics of atovaquone and proguanil for the treatment of uncomplicated falciparum malaria in third-trimester pregnant women. Eur J Clin Pharmacol. 2005;61(8):573–582.
121. Wangboonskul J, White NJ, Nosten F, et al. Single dose pharmacokinetics of proguanil and its metabolites in pregnancy. Eur J Clin Pharmacol. 1993;44(3):247–251.
122. McGready R, Stepniewska K, Seaton E, et al. Pregnancy and use of oral contraceptives reduces the biotransformation of proguanil to cycloguanil. Eur J Clin Pharmacol. 2003;59(7):553–557.
123. McGready R, Keo NK, Villegas L, et al. Artesunate-atovaquone-proguanil rescue treatment of multidrug-resistant Plasmodium falciparum malaria in pregnancy: a preliminary report. Trans R Soc Trop Med Hyg. 2003;97(5):592–594.
124. White NJ, Pukrittayakamee S, Hien TT, et al. Malaria. Lancet. 2014;383(9918):723–735.
125. Goodman CD, Siregar JE, Mollard V, et al. Parasites resistant to the antimalarial atovaquone fail to transmit by mosquitoes. Science. 2016;352(6283):349–353.
126. GlaxoSmithKline. Malarone - prescribing information. 2008 [cited 2018 Apr 28]; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021078s016lbl.pdf
127. Björn P, Anders H. Atovaquone-proguanil use in early pregnancy and the risk of birth defects. Arch Intern Med. 2011;171(3):259–260.
128. Reuvers N, Vial T, Schaefer C, et al. Pregnancy outcome after first trimester exposure to malarone (atovaquone-proguanif): A prospective case-series. Birth Defects Res A Clin Mol Teratol. 2012;94 (5):329.
129. Tan KR, Fairley JK, Wang M, et al. A survey on outcomes of accidental atovaquone–proguanil exposure in pregnancy. Malar J. 2018;17:198.
130. WorldWide Antimalarial Resistance Network. SP Molecular Surveyor. 2018 [cited 2018 Jul 2]; Available from: http://www.wwarn.org/dhfr-dhps-surveyor/
131. Desai M, Hill J, Fernandes S, et al. Prevention of malaria in pregnancy. Lancet Infect Dis. 2018;18(4):e119–e32.
132. Peters PJ, Thigpen MC, Parise ME, et al. Safety and toxicity of sulfadoxine/pyrimethamine: implications for malaria prevention in pregnancy using intermittent preventive treatment. Drug Saf. 2007;30(6):481–501.
133. Hamer DH, Mwanakasale V, MacLeod WB, et al. Two-dose versus monthly intermittent preventive treatment of malaria with sulfadoxine-pyrimethamine in HIV-seropositive pregnant Zambian women. J Infect Dis. 2007;196(11):1585–1594.
134. Nosten F, McGready R. Intermittent presumptive treatment in pregnancy with sulfadoxine–pyrimethamine: a counter perspective. Malar J. 2015;14:248.
135. de Kock M, Tarning J, Workman L, et al. Pharmacokinetics of sulfadoxine and pyrimethamine for intermittent preventive treatment of malaria during pregnancy and after delivery. CPT Pharmacometrics Syst Pharmacol. 2017;6(7):430–438.
136. Edstein MD, Veenendaal JR, Newman K, et al. Excretion of chloroquine, dapsone and pyrimethamine in human milk. Br J Clin Pharmacol. 1986;22(6):733–735.
137. Villegas L, McGready R, Htway M, et al. Chloroquine prophylaxis against vivax malaria in pregnancy: a randomized, double-blind, placebo-controlled trial. Trop Med Int Health. 2007;12(2):209–218.
138. Wolfe MS, Cordero JF. Safety of chloroquine in chemosuppression of malaria during pregnancy. Br Med J Clin Res. 1985;290 (6480):1466–1467.
139. Kimani J, Phiri K, Kamiza S, et al. Efficacy and safety of azithromycin-chloroquine versus sulfadoxine-pyrimethamine for intermittent preventive treatment of Plasmodium falciparum malaria infection in pregnant women in Africa: an open-label, randomized trial. PLoS One. 2016;11(6):e0157045.
140. Akintonwa A, Gbajumo SA, Mabadeje AF. Placental and milk transfer of chloroquine in humans. Ther Drug Monit. 1988;10(2):147–149.
141. Ette EI, Essien EE, Ogonor JI, et al. Chloroquine in human milk. J Clin Pharmacol. 1987;27(7):499–502.
142. Law I, Ilett KF, Hackett LP, et al. Transfer of chloroquine and desethylchloroquine across the placenta and into milk in Melanesian mothers. Br J Clin Pharmacol. 2008;65(5):674–679.
143. Witte AM, Klever HJ, Brabin BJ, et al. Field evaluation of the use of an ELISA to detect chloroquine and its metabolites in blood, urine and breast-milk. Trans R Soc Trop Med Hyg. 1990;84(4):521–525.
144. Deturmeny E, Viala A, Durand A, et al. [Chloroquine transfer to milk. A Case]. Therapie. 1984;39(4):438–440.
145. Ogunbona FA, Onyeji CO, Bolaji OO, et al. Excretion of chloroquine and desethylchloroquine in human milk. Br J Clin Pharmacol. 1987;23(4):473–476.
146. Boelaert JR, Yaro S, Augustijns P, et al. Chloroquine accumulates in breast-milk cells: potential impact in the prophylaxis of postnatal mother-to-child transmission of HIV-1. Aids. 2001;15(16):2205–2207.
147. Motta M, Tincani A, Faden D, et al. Follow-up of infants exposed to hydroxychloroquine given to mothers during pregnancy and lactation. J Perinatol. 2005;25(2):86–89.
148. Costedoat-Chalumeau N, Amoura Z, Huong DL, et al. Safety of hydroxychloroquine in pregnant patients with connective tissue diseases. Review of the Literature. Autoimmun Rev. 2005;4 (2):111–115.

149. Abarientos C, Sperber K, Shapiro DL, et al. Hydroxychloroquine in systemic lupus erythematosus and rheumatoid arthritis and its safety in pregnancy. Expert Opin Drug Saf. 2011;10(5):705–714.
150. Shen PL, Xu JM, Qian XM, et al. [The embryotoxicity of primaquine octylamide in rats]. Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi. 1985;3(3):201–202.
151. Azevedo ENd, Santos AS, Mendes ETR, et al. Efeitos do uso crônico do difosfato de primaquina sobre a prenhez da rata. Revista Brasileira de Ginecologia e Obstetrícia. 1998;20:505–508.
152. Mentzer WC Jr., Collier E. Hydrops fetalis associated with erythrocyte G-6-PD deficiency and maternal ingestion of fava beans and ascorbic acid. J Pediatr. 1975;86(4):565–567.
153. Corchia C, Balata A, Meloni GF, et al. Favism in a female newborn infant whose mother ingested fava beans before delivery. J Pediatr. 1995;127(5):807–808.
154. Perkins RP. Hydrops fetalis and stillbirth in a male glucose-6-phosphate dehydrogenase-deficient fetus possibly due to maternal ingestion of sulfisoxazole; a case report. Am J Obstet Gynecol. 1971;111(3):379–381.
155. Gauthier TW. Methylene blue-induced hyperbilirubinemia in neonatal glucose-6-phosphate dehydrogenase (G6PD) deficiency. J Matern Fetal Med. 2000;9(4):252–254.
156. Yeruchimovich M, Shapira B, Mimouni FB, et al. Neonatal nucleated red blood cells in G6PD deficiency. Am J Perinatol. 2002;19(4):215–219.
157. Cappellini MD, Fiorelli G. Glucose-6-phosphate dehydrogenase deficiency. Lancet. 2008;371(9606):64–74.
158. Thielemans L, Gornsawun G, Hanboonkunupakarn B, et al. Diagnostic performances of the fluorescent spot test for G6PD deficiency in newborns along the Thailand-Myanmar border: A cohort study. Wellcome Open Res. 2018;3:1.
159. Gilder ME, Hanpithakphong W, Hoglund RM, et al. Primaquine pharmacokinetics in lactating women and breastfed infant exposures. Clin Infect Dis. 2018;67(7):1000–1007.
160. Smith JA, Morgan JR, Rachlis AR, et al. Clindamycin in human breast milk. Can Med Assoc J. 1975;112(7):806.
161. Steen B, Rane A. Clindamycin passage into human milk. Br J Clin Pharmacol. 1982;13(5):661–664.
162. Fulton B, Moore LL. Antiinfectives in breastmilkPart III: antituberculars, quinolones and urinary germicides. J Hum Lact. 1993;9(1):43–46.
163. Mitrano JA, Spooner LM, Belliveau P. Excretion of antimicrobials used to treat methicillin-resistant Staphylococcus aureus infections during lactation: safety in breastfeeding infants. Pharmacotherapy. 2009;29(9):1103–1109.
164. Zhang Y, Zhang Q, Xu Z. [Tissue and body fluid distribution of antibacterial agents in pregnant and lactating women]. Zhonghua Fu Chan Ke Za Zhi. 1997;32(5):288–292.
165. Mann CF. Clindamycin and breast-feeding. Pediatrics. 1980;66(6):1030–1031.
166. Cross R, Ling C, Np D, et al. Revisiting doxycycline in pregnancy and early childhood–time to rebuild its reputation? Expert Opin Drug Saf. 2016;15(3):367–382.
167. Hellgren U, Rombo L. Alternatives for malaria prophylaxis during the first trimester of pregnancy: our personal view. J Travel Med. 2010;17(2):130–132.
168. Lutziger H. [Concentration determinations and clinical effectiveness of doxycycline (Vibramycin) in the uterus, adnexa and maternal milk]. Ther Umsch. 1969;26(8):476–480.
169. Morganti G, Ceccarelli G, Ciaffi G. [Comparative concentrations of a tetracycline antibiotic in serum and maternal milk]. Antibiotica. 1968;6(3):216–223.
170. Tokuda G-I, Yuasa M, Mihara S, et al. Clinical study of doxycyclin in obstetrical and gynecological fields. Chemo. 1969;17(2):339–344.
171. Hale TW, Rowe HE. Medications and mothers' milk. 17th ed. New York, NY: Springer Publishing Company; 2017.
172. Saito M, Gilder ME, Nosten F, et al. Methodology of assessment and reporting of safety in anti-malarial treatment efficacy studies of uncomplicated falciparum malaria in pregnancy: A systematic literature review. Malar J. 2017;16:491.
• **A review focused on the assessment and reporting of the safety outcomes in antimalarial efficacy studies in pregnancy.**
173. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3 Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401–406.
174. White NJ. Intermittent presumptive treatment for malaria. PLoS Med. 2005;2(1):e3.
175. Ter Kuile FO, Rw S. Intermittent preventive therapy with sulfadoxine-pyrimethamine during pregnancy: seeking information on optimal dosing frequency. J Infect Dis. 2007;196(11):1574–1576.