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Treatment of uncomplicated and severe malaria during pregnancy

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Over the past 10 years, the available evidence on the treatment of malaria during pregnancy has increased substantially. Owing to their relative ease of use, good sensitivity and specificity, histidine rich protein 2 based rapid diagnostic tests are appropriate for symptomatic pregnant women; however, such tests are less appropriate for systematic screening because they will not detect an important proportion of infections among asymptomatic women. The effect of pregnancy on the pharmacokinetics of antimalarial drugs varies greatly between studies and class of antimalarial drugs, emphasising the need for prospective studies in pregnant and non-pregnant women. For the treatment of malaria during the first trimester, international guidelines are being reviewed by WHO. For the second and third trimester of pregnancy, results from several trials have confirmed that artemisinin-based combination treatments are safe and efficacious, although tolerability and efficacy might vary by treatment. It is now essential to translate such evidence into policies and clinical practice that benefit pregnant women in countries where malaria is endemic. Access to parasitological diagnosis or appropriate antimalarial treatment remains low in many countries and regions. Therefore, there is a pressing need for research to identify quality improvement interventions targeting pregnant women and health providers. In addition, efficient and practical systems for pharmacovigilance are needed to further expand knowledge on the safety of antimalarial drugs, particularly in the first trimester of pregnancy.

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This is the third in a Series of three papers about malaria in pregnancy

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For more on the **Malaria in Pregnancy Consortium** see http://www.mip-consortium.org

Introduction

All malaria infections in pregnancy should be treated promptly with safe and efficacious antimalarial drugs to prevent harmful effects on the mother and fetus.[1,2] Concerns about the potential for harm of new antimalarial treatments on pregnant women or their unborn baby have led to their systematic exclusion from clinical trials, resulting in scarcity of data for their pharmacokinetics, safety, and efficacy during pregnancy,[3–5] particularly for the first trimester.[6,7] However, over the past 10 years,[8] there has been substantial research on malaria in pregnancy by the Malaria in Pregnancy Consortium and others to address gaps in knowledge. Herein, we summarise the results.

Diagnosis

Case management of malaria involves identification of a suspect case, based on the presence of signs or symptoms, diagnostic testing, and treatment, if needed. The accuracy of diagnostic tests depends on parasite density. Microscopy by an experienced and well equipped technician has a detection threshold of 15 parasites per µL of blood,[1] while for rapid diagnostic tests (RDTs), which detect circulating parasite antigens, this threshold can be as low as 200 parasites per µL.[9] Such diagnostic tests might be adequate for pregnant women with malaria symptoms because these individuals usually have parasite densities above the thresholds for detection.[10] However, most infections during pregnancy are asymptomatic, with low parasite densities that are often not detected by microscopy. The public health importance of such infections is controversial because they have been associated with anaemia, reduced mean haemoglobin, low birthweight, and premature births in some studies,[11] but not in others.[12] Intermittent screening and treatment is a potential alternative to intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine–pyrimethamine in areas with high resistance to sulfadoxine–pyrimethamine or low malaria transmission. The effectiveness of such screening and treatment is based on the assumption that currently available tests—specifically RDTs—should be able to identify most infections, but this is probably not true; because of their ability to detect circulating parasite antigens, RDTs might be useful in diagnosing placental malaria, particularly for *Plasmodium falciparum*.[13] In a systematic review of 49 studies, with microscopy of placental blood as the gold standard, RDTs sensitivity was 81% (95% CI 55–93) and specificity was 94% (76–99), whereas PCR had increased sensitivity (94%, 86–98) but decreased specificity (77%, 71–82).[14] However, in Papua New Guinea, more than half of active placenta infections were not diagnosed by RDT, microscopy, or PCR in peripheral blood.[15] Similar results were reported from Mozambique,[16] possibly because of occult placental sequestration.[15] Nevertheless, in Malawi, latent class analysis (which does not assume a gold standard) showed that RDT sensitivity on peripheral blood for diagnosing placental malaria was 92·7%, and specificity was 91·8%.[17] As for peripheral infections, RDTs had similar[18,19] or lower[10] sensitivity than did microscopy, with histidine rich protein 2 (HRP2)-based RDT performing better than plasmodium lactate dehydrogenase-based RDTs.[10,20]

Because of their relative ease of use and good sensitivity and specificity, HRP2-based RDTs are appropriate for symptomatic pregnant women; however, they are less

useful for systematic screening since these tests are unable to diagnose an important proportion of infections among asymptomatic pregnant women. Ultra-sensitive RDT (such as Malaria Ag P.f; Alere, Waltham, MA, USA) should be evaluated for the detection of low-density infections in pregnant women.

Treatment of uncomplicated malaria

First trimester

For *P falciparum* malaria infections during the first trimester, WHO recommends quinine with clindamycin for 7 days (or quinine alone if clindamycin is not available) and, in situations of failure or unavailability, an artemisinin-based combination therapy (ACT) or oral artesunate with clindamycin for 7 days.[2] This recommendation is based on data from 700 pregnant women exposed to artemisinin derivatives during the first trimester, and excludes at least a 4·2-fold increase in risk of major congenital defects.[2] However, the Malaria Policy Advisory Committee has recommended that these guidelines should be revised on the basis of meta-analysis findings.[21,22]

Malaria caused by *Plasmodium* species other than *P falciparum* (non-falciparum malaria) should be treated with chloroquine; quinine is recommended for chloroquine-resistant infections.[2]

Second and third trimester

Guidelines for the treatment of *P falciparum* malaria in the second and third trimester are the same as for non-pregnant adults; this means any ACTs that are recommended as first-line treatment—namely, artemether–lumefantrine, artesunate–amodiaquine, artesunate–mefloquine, dihydro-artemisinin–piperaquine, or artesunate plus sulfadoxine–pyrimethamine—can be used in pregnancy.[2] A systematic review[23] of 16 randomised controlled trials done between 1998 and 2009 presented ten trials testing ACTs (three trials of artesunate plus sulfadoxine–pyrimethamine, two of artemether–lumefantrine, three of artesunate–mefloquine, one of dihydroartemisinin–piperaquine, and one of artesunate with atovaquone–proguanil) versus either combinations without artemisinins or monotherapies. In most trials, ACTs had a PCR-adjusted efficacy of more than 90%, with the exception of artemether–lumefantrine at the Thai–Myanmar border,[23] which had an efficacy of 87% at day 42 that was attributed to low drug concentrations and low antimalarial immunity.[24] A systematic review and meta-analysis comparing the efficacy, safety, and tolerance of ACTs with that of quinine and other non-ACT antimalarial drugs (azithromycin plus sulfadoxine–pyrimethamine or amodiaquine plus sulfadoxine–pyrimethamine) included six trials done between 1995 and 2009; three studies were from sub-Saharan Africa (Malawi, Tanzania, and Uganda) and three were from Asia (Thailand), and all of them were included in the previous review,[23] except the study in Uganda.[25] ACTs were significantly more efficacious than was oral quinine in Thailand and had similar efficacy to non-ACTs in Africa. Birth outcomes were similar between treatment arms, with the exception of mean birthweight, which was significantly higher in ACT recipients than in non-ACT recipients, indicating ACTs might clear parasites (including those in the placenta) more efficiently than do other treatments.[26] Furthermore, artemether–lumefantrine was associated with decreased rates of moderate to high-grade haemozoin deposition in the placenta compared with oral quinine in Uganda (13·3% *vs* 25·8%), indicating a protective effect against placental malaria.[27]

A large multicentre randomised open-label trial testing four ACTs (artemether–lumefantrine, artesunate–amodiaquine, artesunate–mefloquine, and dihydro-artemisinin–piperaquine) in pregnant women with *P falciparum* malaria was done between 2010 and 2013 in four sub-Saharan African countries (Burkina Faso, Ghana, Malawi, and Zambia). In total, 3428 pregnant women were recruited and followed up until day 63 after treatment and again at delivery. PCR-adjusted cure rates for all ACTs ranged from 94·8% to 99·2%, within the prespecified equivalence margin. Nevertheless, the cure rates in the artemether–lumefantrine group were significantly lower than for the other treatments, which had similar high efficacy.[28] The significantly lower unadjusted cure rates in the artemether–lumefantrine group (52·5%) than in the other treatment groups (artesunate–amodiaquine 82·3%; artesunate–mefloquine 73·8%; dihydroartemisinin–piperaquine 86·9%) show that, in areas of intense transmission, dihydroartemisinin–piperaquine might be preferable to artemether–lumefantrine because of its longer post-treatment prophylactic period.

A few smaller trials done in sub-Saharan Africa (Nigeria in 2015[29] and Uganda in 2016[30]) have also shown the high efficacy of ACTs.

In southern Papua, Indonesia, in 2006, dihydro-artemisinin–piperaquine became the first-line treatment for malaria in pregnant women in their second and third trimester; as a result, the number of congenital malaria cases decreased from 3·2% to 0·2%, and there have been no cases since 2008.[31] The implementation of dihydroartemisinin–piperaquine also resulted in a decreased risk of malaria at delivery, early neonatal deaths,[32] severe maternal anaemia, and low birthweight.[33]

Although chloroquine can be used to treat non-falciparum malaria,[1] *Plasmodium vivax* resistance emerged in the 1980s in New Guinea and has spread to the Indonesian archipelago and Mekong region.[34] Most antimalarial drugs with activity against *P falciparum* have intrinsic activity against the asexual stages of *P vivax*, except antifolate drugs.[34] Therefore, *P vivax* malaria can be treated with any ACT that is effective against *P falciparum*, with the exception of artesunate plus sulfadoxine–pyrimethamine.[2] Although ACTs rapidly clear the asexual stages of *P vivax*, there is high variability in the occurrence of recurrent infection between 28 days and 63 days post-treatment.[34] Primaquine—which is the only available drug effective against the liver stages of the parasite's life cycle—is

	Participants	Effects in pregnancy
Artesunate		
Thailand	24 pregnant women[38]	Exposure to dihydroartemisinin decreased (9 times lower C_{max} and 4 times lower $AUC_{0-24\,h}$ when corrected for dose) in pregnant women compared with in historical controls
Thailand	20 pregnant women and 15 post-partum women[39,40]	Exposure to dihydroartemisinin decreased by 23% in pregnant women compared with in post-partum women
Democratic Republic of the Congo	26 pregnant women, 26 post-partum women, and 25 non-pregnant women[41,42]	Exposure to dihydroartemisinin decreased by 42% in pregnant women compared with in non-pregnant women
Burkina Faso	24 pregnant women and 24 non-pregnant women[43]	No difference in exposure to dihydroartemisinin in pregnant women compared with in non-pregnant women
Summary	..	Contradictory results; generally decreased exposure reported in pregnant women compared with in non-pregnant women
Artemether		
Uganda	30 pregnant women and 30 non-pregnant women[44]	No difference in exposure to dihydroartemisinin in pregnant women compared with in non-pregnant women
Tanzania	33 pregnant women and 22 non-pregnant women[45]	No difference in exposure to dihydroartemisinin in pregnant women compared with in non-pregnant women
Uganda	21 pregnant women[45,46]	Exposure to dihydroartemisinin decreased in pregnant women compared with in historical controls
Thailand	13 pregnant women[47]	Exposure to dihydroartemisinin was 50% lower in pregnant women than in male patients studied previously
Summary	..	Contradictory results; generally no difference in exposure reported in pregnant women compared with in non-pregnant women
Dihydroartemisinin		
Papua New Guinea	32 pregnant women and 33 non-pregnant women[48]	No difference in exposure to dihydroartemisinin in pregnant women compared with in non-pregnant women
Thailand	24 pregnant women and 24 non-pregnant women[49,50]	Exposure to dihydroartemisinin decreased by 38% in pregnant women compared with in non-pregnant women
Uganda	31 pregnant women and 30 non-pregnant women[51]	Exposure to dihydroartemisinin decreased by 47% in pregnant women compared with in non-pregnant women
Summary	..	Contradictory results; no difference and decreased exposure reported in pregnant women compared with in non-pregnant women
Chloroquine		
Papua New Guinea	30 pregnant women and 30 non-pregnant women[52]	Exposure to chloroquine decreased by 34% in pregnant women compared with in non-pregnant women
Thailand	12 pregnant women and 15 non-pregnant women[53]	No difference in exposure to chloroquine in pregnant women compared with in non-pregnant women
Tanzania	49 pregnant women[54]	Exposure to chloroquine decreased by about 30–40% in pregnant women compared with in historical controls
Summary	..	Contradictory results; no difference and decreased exposure reported in pregnant women compared with in non-pregnant women
Amodiaquine		
Thailand	24 pregnant women and 18 post-partum women[55,56]	No difference in exposure to amodiaquine and desethylamodiaquine in pregnant women compared with in post-partum women
Summary	..	No difference in exposure reported in pregnant women compared with in non-pregnant women
Piperaquine		
Papua New Guinea	32 pregnant women and 33 non-pregnant women[48]	Exposure to piperaquine decreased by 42% in pregnant women compared with in non-pregnant women
Thailand	24 pregnant women and 24 non-pregnant women[49,50]	No difference in exposure to piperaquine in pregnant women compared with in non-pregnant women
Sudan	12 pregnant women and 12 non-pregnant women[57,58]	No difference in exposure to piperaquine in pregnant women compared with in non-pregnant women
Uganda	31 pregnant women and 30 non-pregnant women[51]	Exposure to piperaquine decreased by 40% in pregnant women compared with in non-pregnant women
Summary	..	Contradictory results; no difference and decreased exposure reported in pregnant women compared with in non-pregnant women

(Table 1 continues on next page)

	Participants	Effects in pregnancy
(Continued from previous page)		
Mefloquine		
Burkina Faso	24 pregnant women and 24 non-pregnant women[43]	No difference in exposure to mefloquine in pregnant women compared with in non-pregnant women
Burkina Faso	Nine pregnant women and eight non-pregnant women[59]	No difference in exposure to mefloquine in pregnant women compared with in non-pregnant women
Thailand	20 pregnant women[60]	Exposure to mefloquine decreased by approximately 50% in pregnant women compared with in historical controls
Summary	..	Contradictory results; generally no difference in exposure reported in pregnant women compared with in non-pregnant women
Quinine		
Uganda	22 pregnant women[45,61]	Exposure to quinine was approximately 50% lower in pregnant women than it was in historical controls
Sudan	Eight pregnant women and eight non-pregnant women[62]	No difference in exposure to quinine in pregnant women compared with in non-pregnant women
Sudan	Nine pregnant and eight non-pregnant women[63]	No difference in exposure to quinine in pregnant women compared with in non-pregnant women
Summary	..	Contradictory results; generally no difference in exposure reported in pregnant women compared with in non-pregnant women
Lumefantrine		
Uganda	30 pregnant women and 30 non-pregnant women[39]	No difference in exposure to lumefantrine in pregnant women compared with in non-pregnant women
Tanzania	33 pregnant women and 22 non-pregnant women[44]	Exposure to lumefantrine decreased by 34% in pregnant women compared with in non-pregnant women
Uganda	26 pregnant women and 17 non-pregnant women[45]	No difference in exposure to lumefantrine in pregnant women compared with in non-pregnant women
Thailand	13 pregnant women[47]	Exposure to lumefantrine was lower in pregnant women than it was in historical controls (mostly males)
Uganda	116 pregnant women and 17 non-pregnant women[64]	No difference in exposure to lumefantrine in pregnant women compared with in non-pregnant women
Thailand	103 pregnant women[65]	Exposure to lumefantrine decreased by about 20% in pregnant women compared with in historical controls
Summary	..	Contradictory results; generally no difference in exposure reported in pregnant women compared with in non-pregnant women
Sulfadoxine		
Papua New Guinea	30 pregnant women and 30 non-pregnant women[66]	Exposure to sulfadoxine decreased by 33% in pregnant women compared with in non-pregnant women
Kenya	33 pregnant women and 11 post-partum women[67]	Exposure to sulfadoxine decreased by 43% in pregnant women compared with in post-partum women
Mali and Zambia	43 pregnant women and 40 post-partum women[68]	No difference in exposure to sulfadoxine in pregnant women compared with in post-partum women
Uganda	87 pregnant women and 34 non-pregnant women[69]	Exposure to sulfadoxine decreased by 82% in pregnant women compared with in non-pregnant women
Summary	..	Contradictory results; generally decreased exposure reported in pregnant women compared with in non-pregnant women
Pyrimethamine		
Papua New Guinea	30 pregnant women and 30 non-pregnant women[66]	Exposure to pyrimethamine decreased by 32% in pregnant women compared with in non-pregnant women
Kenya	33 pregnant women and 11 post-partum women[67]	No difference in exposure to pyrimethamine in pregnant women compared with in post-partum women
Mali and Zambia	43 pregnant women and 40 post-partum women[68]	Exposure to pyrimethamine decreased by 31% in pregnant women compared with in post-partum women
Uganda	87 pregnant women and 34 non-pregnant women[69]	Exposure to pyrimethamine decreased by 34% in pregnant women compared with in non-pregnant women
Summary	..	Contradictory results; no difference, increased and decreased exposure reported in pregnant women compared with in non-pregnant women

Relative difference in exposure calculated as ($AUC_{comparison}$ – $AUC_{pregnancy}$) / $AUC_{comparison}$ or as indicated.

Table 1: **Pharmacokinetic summary by drug and country**

contraindicated in pregnant women and during breastfeeding, because of the risk of haemolysis if the offspring is glucose-6-phospate dehydrogenase deficient;[34] primaquine can be administered when the woman has stopped breastfeeding.

Treatment of complicated malaria

Pregnant women have a higher risk of developing severe malaria. This is particularly true in areas with low transmission of malaria, where severe malaria is often complicated by pulmonary oedema and hypoglycaemia.[2] Intensive care and prompt parenteral antimalarial treatment are crucial to the mother's survival.[1] A review on the treatment of severe malaria in all trimesters of pregnancy identified ten studies that reported clinical outcomes.[35] The review supports the WHO recommendation for intravenous artesunate as the drug of choice or, if unavailable, intramuscular artemether.[2] Absorption of artemether is less predictable for intramuscular administration, especially in patients with cardiovascular collapse.[1] Parenteral quinine, although associated with recurrent hypoglycaemia, can be used when artesunate or artemether are not available.[2]

Until controlled clinical trials are conducted, severe malaria that is caused by species other than *P falciparum* should be managed in the same way as severe *P falciparum* malaria (ie, in intensive care settings with intravenous artesunate or quinine).[34]

Pharmacokinetics

Pregnancy is associated with various physiological changes that can alter the absorption, disposition, metabolism, and excretion of drugs.[36] These pregnancy-related changes in pharmacokinetic properties could result in overexposure or underexposure to antimalarial drugs. Overexposure might lead to maternal and fetal toxicity and underexposure could cause therapeutic failures, resulting in poor pregnancy outcomes, maternal death, and increased risk of drug resistance.[36,37] Reports of the pharmacokinetics of antimalarial drugs in pregnancy are often contradictory and based on small studies without non-pregnant control patients (table 1). Controlled prospective pharmacokinetic studies are needed to evaluate the effect of pregnancy. Ideally, non-pregnant controls should be matched by sex, malaria infection status, and age to control for confounding covariates, and evaluated via pharmacokinetic modelling to quantify potential pregnancy-specific effects.

Artemisinins

Systemic exposure to artesunate and its active metabolite, dihydroartemisinin, after oral administration of artesunate, was substantially lower in pregnant women with *P falciparum* malaria on the Thai–Myanmar border than in historical[38] and post-partum controls.[39,40] In one of these studies, malaria and pregnancy had opposite effects on the absorption of orally administered artesunate; malaria increased the oral bioavailability of artesunate by 87%, whereas pregnancy decreased the oral bioavailability by 23%.[39] However, there was no evidence of pregnancy-related alterations of the pharmacokinetic properties of artesunate or dihydroartemisinin after intravenous administration, suggesting that standard treatment recommendations for severe malaria apply to pregnant women. A study carried out in Kinshasa, Democratic Republic of the Congo, which compared women during pregnancy and postpartum with non-pregnant controls, showed that drug exposure changed in pregnant women (42% decrease in exposure to dihydroartemisinin) after oral administration of artesunate.[41,42] However, no difference in exposure to dihydroartemisinin was seen in pregnant and non-pregnant women in Burkina Faso after oral artesunate treatment.[43]

Two clinical studies in pregnant women and matched non-pregnant controls in Uganda[30] and Tanzania[44] reported that the pharmacokinetic properties of artemether and its active metabolite, dihydroartemisinin, were unaltered after oral administration of artemether. However, studies that recruited only pregnant women showed lower drug exposures in pregnant women than did studies of historical controls.[45–47,61]

Contradictory results have also been presented regarding systemic drug exposure to dihydroartemisinin after oral administration in pregnant women and matched non-pregnant controls.[48–51] In Thailand and Uganda, drug exposure was substantially lower (Thailand 38% lower, Uganda 47% lower) in pregnant women than in non-pregnant women,[49] whereas in Papua New Guinea pharmacokinetic properties in pregnant women were unaltered.[48] Therefore, it might be necessary to increase doses of ACTs for pregnant women, but more data are needed. A systematic review reached similar conclusions.[70]

4-amino-quinolines

Drug exposure to chloroquine and its main metabolite, desethylchloroquine, was significantly reduced (chloroquine 25% reduced, desethylchloroquine 45% reduced) in pregnant women, compared with in age-matched non-pregnant women, in Papua New Guinea when receiving three daily doses (450 mg/day) of chloroquine as IPTp.[52] This difference was due to increased elimination of both chloroquine and desethylchloroquine during pregnancy. However, in another study, pharmacokinetic parameters of chloroquine or desethylchloroquine were not different between pregnant and non-pregnant Karen women with *P vivax* malaria.[53]

There were no differences in the pharmacokinetic properties of amodiaquine or desethylamodiaquine, its main metabolite, between pregnant women in the second and third trimesters with *P vivax* malaria and the same women at 3 months postpartum.[55] Population pharmacokinetic modelling showed that pregnancy did

not have a clinically significant effect on the pharmacokinetics of amodiaquine or desethylamodiaquine, with no need for dose adjustment.[56]

There have been contradictory results regarding the pharmacokinetic properties of piperaquine in pregnancy. There was no significant difference in total drug exposure to piperaquine between pregnant and non-pregnant women with *P falciparum* malaria in Thailand.[50] Population pharmacokinetic modelling at the population-level showed similar effects of piperaquine on the relative bioavailability and elimination, resulting in a net effect of unaltered drug exposure, but a shorter elimination half-life in pregnant women.[49] Similar results were obtained in pregnant and age-matched and weight-matched non-pregnant Sudanese women with *P falciparum* malaria.[57,58] However, exposure to piperaquine was about 40% lower in pregnant women than it was in non-pregnant women in Papua New Guinea[48] and Uganda.[51]

Quinoline methanols and related drugs

There were no relevant differences in exposure to mefloquine between pregnant women in their second and third trimester and matched non-pregnant women with *P falciparum* malaria in Burkina Faso when these women were treated with artesunate–mefloquine.[43] However, peak concentrations of mefloquine were significantly lower in pregnant women than in non-pregnant women with *P falciparum* malaria treated with a single oral dose of mefloquine.[59] Similarly, a dose-finding study on the Thai–Myanmar border suggests that drug exposure to mefloquine might be decreased in late pregnancy.[60]

Mean pharmacokinetic parameters of quinine and its metabolites were not significantly different between Sudanese pregnant and non-pregnant women with *P falciparum* malaria who received a single dose of quinine hydrochloride (as intravenous infusion over 2 h), suggesting that no dose adjustment is required in pregnancy.[62] However, in these women, exposure to quinine during clinical malaria was higher than it was during the convalescence phase.[63] Similarly, in Uganda, increased exposure to quinine during clinical malaria, compared with the convalescence phase, was reported in pregnant women with *P falciparum* malaria who were treated with oral quinine. Nevertheless, drug exposure in pregnant women was only about half of that in non-pregnant patients.[61]

Systemic drug exposure to lumefantrine is generally lower in pregnant women than in non-pregnant women treated with artemether–lumefantrine for *P falciparum* malaria.[44,64,65] These studies showed a decrease of about 30% in concentrations of lumefantrine on day 7 in pregnant versus non-pregnant patients. However, one study in rural Uganda showed no differences in exposure to lumefantrine between pregnant women and non-pregnant women with *P falciparum* malaria.[30]

Antifolates

In Papua New Guinea, exposures to sulfadoxine and pyrimethamine were significantly lower in pregnant women than in non-pregnant women.[66] A study in Kenya evaluated the pharmacokinetic properties of sulfadoxine and pyrimethamine in 33 pregnant women and 11 women post partum and had similar results for sulfadoxine, while pyrimethamine was unaffected by pregnancy.[67] A multicentre study (Mali, Mozambique, Sudan, and Zambia) also showed that exposure to sulfadoxine was lower during pregnancy than it was during post partum while reporting higher pyrimethamine exposure during pregnancy.[68] Pharmacokinetic data for both drugs were highly variable among the study sites and did not suggest that dose adjustment was necessary in pregnancy.[68]

Drug safety

To date, issues with the methodology of studies have prevented firm conclusions on the safety of antimalarial drugs in pregnancy (table 2). Studies are often underpowered to detect rare safety outcomes and small differences. The trial design often covers a short or sporadic follow-up period[91] and there is not enough statistical power to adjust for uncontrolled confounders, such as severity of disease or presence of sexually transmitted infections, or both, emphasising the need for continuous safety monitoring.

Artemisinin derivatives and partner drugs

In pregnant rats on gestational day 10, artemisinin derivatives have embryotoxic effects (death, cardiac malformations, and long bone malformations) due to the death of circulating embryonic erythroblasts.[92] In human beings, dihydroartemisinin is responsible for erythrotoxicity.[93,94] In rats, embryos were most sensitive to the lethal effects of artesunate at gestational days 10–14; the corresponding gestational age in human beings is about 3–9 weeks after conception.[95] Artemisinins concentrate in infected red blood cells while malaria causes hypoferraemia.[96] Therefore, malaria might protect against artemisinin-induced decreases in the number of reticulocytes by reducing the concentrations of active drug or ferrous iron (which activates the drug to toxic free radicals), or both, in target tissues; such protection by malaria against artesunate-induced toxicity has been seen in rats. This finding could also be true for embryotoxicity, which would mean that pregnant women without malaria would be at greater risk of artemisinin-induced embryotoxicity.[95]

A meta-analysis on 1664 pregnancies that were followed up after treatment with either artemisinin or quinine during the first trimester had no differences in the risk of miscarriage, stillbirth, or major congenital malformations.[22] Risk of miscarriage was similar between women treated with artemisinins during the first trimester and those not treated with an antimalarial; the

	Safety profile
Artemisinin derivatives and partner drugs	
Artemisinin derivatives	Artemisinin derivatives in general are well tolerated; concerns regarding safety on pregnancy have limited its use in first trimester; recent studies reported no differences in the risk of miscarriage, stillbirth, or major congenital malformations between artemisinins and quinine used during first trimester[22,71]
Artemether–lumefantrine	Artemether–lumefantrine is well tolerated;[28] first trimester of pregnancy: no increase in risk of perinatal death, neonatal death, or stillbirth;[72] second and third trimester: no increase in adverse pregnancy outcomes[73]
Amodiaquine–artesunate	Amodiaquine–artesunate has been associated with general weakness, vomiting, dizziness, and nausea but without increased risk of miscarriage, stillbirth, or major congenital malformations[28,74,75]
Dihydroartemisinin–piperaquine	Dihydroartemisinin–piperaquine is well tolerated;[28,50,57,58,76–78] concerns regarding prolongation of the QT interval were raised; more studies are needed to understand the clinical significance of this event in pregnant women[77–79]
Mefloquine–artesunate	Mefloquine–artesunate was less well tolerated when compared with other combinations (artemether–lumefantrine or dihydroartemisinin–piperaquine);[28] pregnancy outcomes similar to those of other antimalarial treatments[28]
Sulfadoxine–pyrimethamine–artesunate	Sulfadoxine–pyrimethamine–artesunate seemed safe and well tolerated[80–82]
Mefloquine	Prevalence of birth defects and fetal loss are simlar to background rates in pregnant women exposed to mefloquine;[83] mefloquine is reported to be less well tolerated (increased risk of dizziness and vomiting) than sulfadoxine–pyrimethamine when used for prevention of malaria; when mefloquine alone was used as intermittent preventive treatment, incidence of spontaneous abortions, stillbirths, and congenital anomalies did not differ significantly compared to sulfadoxine–pyrimethamine[84]
Sulfadoxine–pyrimethamine	When given as an intermittent preventive treatment in pregnancy, sulfadoxine–pyrimethamine does not increase risk of teratogenesis;[85] sulfadoxine–pyrimethamine should not be administered concurrently with co-trimoxazole given their redundant mechanisms of action and synergistic worsening of adverse drug reactions;[86] no clinical association between sulfadoxine–pyrimethamine and kernicterus has been reported[85]
Quinine	Quinine is less well tolerated when comparing with other antimalarials and can cause hypoglycaemia and tinnitus, particularly in the second and third trimester;[5,87] prolongation of the QT interval with no significant cardiotoxicity has been reported[88]
Chloroquine	Chloroquine has been described as safe throughout pregnancy;[89] risk of miscarriage was similar for women treated with chloroquine, quinine, or artesunate[90]

Table 2: **Safety profiles of antimalarials**

risk was significantly higher for women treated with quinine than for those not treated with an antimalarial drug.[22,97] In Thailand, the risk of miscarriage among women attending antenatal clinics between 1986 and 2010 was not significantly different to the risk in those treated between 6 weeks and 12 weeks of gestation with artesunate (31%), quinine (27%), or chloroquine (26%; p=0·71).[90] The risk of miscarriage associated with malaria outweighed any adverse effects from treatment with antimalarial drugs, including artemisinins.[90]

In Thailand,[71] pregnant women in their first trimester who were exposed to either artemisinins or quinine had a similar risk of miscarriage. Consideration of only exposure during the embryo-sensitive window (6–13 weeks gestation) showed that the occurrence of congenital malformations for artemisinins or quinine was similar, although the sample size was small (109 pregnancies for artemisinins, 641 pregnancies for quinine). In Kenya,[98] first trimester exposure to artemisinins was reported in 299 (26%) of 1134 pregnant women, in 178 (8%) of 2167 women in Tanzania,[99] in 156 (16%) of 1001 women in Zambia,[100] and in 96 (9%) of 1072 women in Rwanda.[101] In Kenya,[98] the risk of miscarriage was higher among women treated with artemisinins than in women with no exposure to antimalarial drugs; however, this increase was not seen when analysis was restricted to exposure during the embryo-sensitive period, or when women treated with quinine were compared. In Tanzania,[99] adverse pregnancy outcomes (miscarriage, stillbirth, or prematurity) were more common in women treated with quinine than in women treated with any other antimalarial drug, including artemether–lumefantrine. In Zambia,[100] first trimester exposure to antimalarial drugs was not associated with adverse pregnancy outcomes.

A review of artemether–lumefantrine use in sub-Saharan Africa[72] showed that receipt of this treatment in the first trimester of pregnancy did not increase the risk of perinatal or neonatal death or stillbirth. Infant neurodevelopment, birthweight, and overall incidence of birth defects were also similar, irrespective of treatment with artemether–lumefantrine or other antimalarial drugs during the first trimester. All cases of miscarriage in the artemether–lumefantrine exposure group were in patients who had received treatment during the first trimester, although in most cases there were confounding factors.[72] Preclinical data on lumefantrine alone did not show any embryotoxicity.[36] Nevertheless, artemether–lumefantrine is still not recommended for the treatment of malaria during the first trimester of pregnancy unless quinine, with or without clindamycin, has failed or is unavailable.

A systematic review and meta-analysis[102] of second and third trimester exposure to ACTs in studies in Africa and Asia showed that the risk of miscarriage and congenital anomalies is similar among women in the second or third trimester of pregnancy who were treated with artemisinins and women treated with quinine or other

non-artemisinin antimalarial drugs. The analysis also showed that the risk of stillbirth was lower in women who were treated with ACT than in those treated with quinine, possibly reflecting a higher efficacy of artemisinin treatment.[102]

Another systematic review showed that, in the second and third trimester, artemether–lumefantrine was not associated with increased adverse pregnancy outcomes as compared with quinine or sulfadoxine–pyrimethamine, showed improved tolerability relative to quinine, and its efficacy was non-inferior to quinine.[73]

Between 1948 and 1990, six studies reported amodiaquine use in pregnancy; only one study had adverse events, but information on these events was scarce.[103] A subsequent study showed that amodiaquine, given alone or in combination with sulfadoxine–pyrimethamine during the second or third trimester, was not associated with liver toxicity or bone marrow depression.[104] In Ghana, pregnant women treated with amodiaquine alone or in combination with sulfadoxine–pyrimethamine had an increased frequency of mild adverse events compared with those treated with sulfadoxine–pyrimethamine alone; there was no difference in miscarriages, stillbirths, neonatal jaundice, and neonatal deaths between the groups.[105] At standard doses, amodiaquine does not cause developmental malformations of the embryo or fetus and the adverse events seen during pregnancy are no more common than those associated with *P falciparum* malaria in pregnancy.[106] Since this study[106] was published, a smaller study reported that amodiaquine is safe and reasonably well tolerated.[55] Amodiaquine–artesunate was not associated with adverse birth outcomes in a 2009 study in Tanzania.[74] Similarly, the proportion of women who reported adverse events during the 7 days after treatment did not differ significantly between treatment groups (IPTp with sulfadoxine–pyrimethamine, and treatment with sulfadoxine–pyrimethamine or amodiaquine–artesunate) with the exception of general weakness, which was slightly more common in women treated with amodiaquine–artesunate.[75]

Dihydroartemisinin–piperaquine was well tolerated and had an acceptable safety profile in one arm of a trial in which more than 800 African pregnant women were treated in the second and third trimester.[28] These results are similar to those from other smaller studies done in Asia[50,76] and Africa.[57,58] Although dihydroartemisinin–piperaquine can cause prolongation of the QT interval,[79] no clinically significant prolongation of the QT interval was seen on 42 pregnant women receiving dihydroartemisinin–piperaquine.[77,78]

Initial concerns regarding the association between mefloquine and stillbirth came from a retrospective analysis in Thailand.[107] This finding was not supported by earlier studies that evaluated mefloquine for treatment of malaria in pregnancy, nor by later studies on mefloquine–artesunate.[108–110] The prevalence of birth defects and fetal loss were similar to background rates in 2506 pregnant women exposed to mefloquine.[83] In 850 African women in the second and third trimester of pregnancy who had *P falciparum* malaria, mefloquine–artesunate was less well tolerated than was artemether–lumefantrine and dihydroartemisinin–piperaquine, and drug-related adverse events were more common with mefloquine–artesunate than with artemether–lumefantrine or dihydroartemisinin–piperaquine; pregnancy outcomes were similar to other antimalarial treatments.[28] When mefloquine alone was used as IPTp, incidence of spontaneous abortions, stillbirths, and congenital anomalies did not differ significantly from incidence in the sulfadoxine–pyrimethamine groups, although adverse events were more common.[84] Adverse events were common, but mostly minor, in a study of pregnant Beninese women; 61 (65%) of 94 HIV-positive women and 300 (78%) of 385 HIV-negative women to whom two doses of mefloquine was given as IPTp had adverse events. Notably, mefloquine tolerability was better in HIV-positive women, a finding that might be explained by these women being more familiar with adverse events and thus less prone to report them.[111,112] In two studies[113,114] for prevention of malaria in HIV-positive and HIV-negative women in Africa, mefloquine was less well tolerated than was sulfadoxine–pyrimethamine. In the study of HIV-positive women,[113] the viral load and frequency of mother to child transmission of HIV was higher in the mefloquine group, but this result needs to be confirmed.

Sulfadoxine–pyrimethamine has been used extensively in pregnancy for treatment and IPTp, but formal safety studies are scarce.[36] Pyrimethamine causes dose-dependent embryotoxicity in rats, but not at human-equivalent doses.[87] In a case-control study, mothers whose babies had cleft palate had a higher exposure to sulfonamides than did controls.[87] Nevertheless, although use of folate antagonists in the first trimester is associated with neural tube defects, large case-control studies have shown that sulfadoxine–pyrimethamine given as IPTp does not increase the risk of teratogenesis.[85] In Malawi[80] and Sudan,[81] sulfadoxine–pyrimethamine plus artesunate given to pregnant women with *P falciparum* malaria was safe and well tolerated, although the sample size in both countries was small. Similarly, in The Gambia, exposure to sulfadoxine–pyrimethamine and a single dose of artesunate in pregnant women during a mass drug administration programme did not have any teratogenic, or any other harmful, effects.[82] Sulfadoxine–pyrimethamine should not be given concurrently with co-trimoxazole because of their redundant mechanisms of action and synergistic worsening of adverse drug reactions.[86] No clinical association between sulfadoxine–pyrimethamine and kernicterus has been reported.[85]

Quinine

The use of quinine in pregnancy is generally thought to be safe, and it is not associated with poor birth outcomes.[36]

Quinine causes prolongation of the QT interval, but no significant cardiotoxicity has been seen in large prospective studies.[88] Furthermore, quinine can sometimes cause hypoglycaemia, particularly in the second and third trimester, even in uncomplicated malaria.[5] In Uganda, the percentage of patients treated for uncomplicated malaria during pregnancy with at least one adverse event (most commonly tinnitus) was significantly higher in the quinine than it was in the artemether–lumefantrine arm.[25]

Chloroquine

Chloroquine has been described as safe throughout pregnancy.[89] Although chloroquine causes prolongation of the QT interval, no significant cardiotoxicity was reported in large prospective studies.[88] A study in Thailand showed that the risk of miscarriage was similar among women treated with chloroquine, quinine, or artesunate.[90]

Access to treatment

Despite wide-scale adoption of the 2006 WHO recommendations[115] to use ACTs to treat uncomplicated malaria in the second and third trimester of pregnancy, access to parasitological diagnosis or appropriate antimalarial treatment remains low in many countries and regions. In a systematic review of women's access and provider practices, case management practices among health-care providers in the public, private, and retail sectors were generally poor.[116] Reliance on clinical diagnosis and poor adherence to treatment policy was consistently reported across different settings.[116] Adherence to treatment policy in the first trimester of pregnancy was significantly lower (28%) than in other trimesters (72%).[116] ACTs, which are currently contraindicated in the first trimester,[22,115] were commonly prescribed either with quinine (recommended policy)[116–119] or as monotherapy.[120] In western Kenya, correct prescription was seen in only five (24%) of 21 women in the first trimester who exited health facilities and in none of the 37 simulated clients attending drug outlets. In the second or third trimester, 48 (65%) of 74 pregnant women leaving health facilities and 15 (40%) of 38 women who visited drug outlets (simulated) had a correct prescription. Notably, 18 (49%) of 37 women in the first trimester who went to drug outlets were prescribed artemether–lumefantrine.[118] Drugs no longer recommended for treatment of *P falciparum* malaria in Africa were widely prescribed for women in all trimesters, including sulfadoxine–pyrimethamine (which is restricted for use as IPTp or prevention only) in Nigeria[117,119–121] and Kenya,[118] and chloroquine in Nigeria.[117,119,121] Use of artemether and artesunate monotherapies were widely reported in Nigeria[117,119–121] and in Uganda.[122]

Correct treatment practices among health providers were associated with knowledge,[121,122] training,[116,118] availability of guidelines,[122] and facility type (public *vs* private, or drug shops).[116,118] Prescribing practices were affected by concerns over side-effects, safety, availability, patient preference, and cost.[116] This research highlights the need for countries to provide quality training, guidelines, and job aids to all health professionals and other providers, particularly drug shops in the community, and to ensure both diagnostic tools and recommended treatments are available at all levels of the health system. Evidence for quality improvement initiatives that target public and private providers are also needed, alongside legislation to regulate which antimalarial drugs are licensed for sale.

Although pregnant women often report bouts of malaria, anthropological research has highlighted that their understanding of malaria symptoms overlap only partly with biomedical definitions and women can find it difficult to distinguish suspected malaria from pregnancy-related symptoms.[123–126] Such confusion contributed to delays in women seeking treatment in Mali and Kenya.[127] Women's choice of health-care provider was influenced by severity and duration of malaria episode,[123,128] knowledge and perceptions of drug safety, drug availability, and cost and perceptions of health-care services,[116,127] with the use of non-biomedical remedies—homemade or from a local healer—reported in Mali,[127] Nigeria,[129] South Sudan,[128] India,[130] and Papua New Guinea.[131] Social relationships influenced treatment seeking behaviour and some women, particularly younger women, sought advice or assistance from relatives.[123,126] The existence of self-treatment, which is typically prompted by high costs of drugs or diagnostic tests, irregular drug supplies at health facilities, or previous poor quality care, or a combination, highlights the need for clear advice on antimalarial drugs and doses that are safe during pregnancy to be made widely available.[123]

Conclusions and future directions

Over the past 10 years, the Malaria in Pregnancy Consortium and other research groups have carried out extensive research to improve the control of malaria in pregnancy, focusing on priorities outlined previously.[132] Evidence on the treatment of malaria during pregnancy has increased substantially. Malaria in pregnancy can be diagnosed by HRP2-based RDTs; available ACTs can be used for the treatment of malaria during the second and third trimester of pregnancy; and WHO might revise the guidelines on the use of artemisinins in the first trimester of pregnancy. This evidence needs to be translated into policy. However, poor quality delivery of health services across public, private, and retail sectors in most endemic regions shows that there is a pressing need for research to identify interventions for quality improvement that target users and providers. The priorities for policy implementation include health provider training on national policy guidelines for diagnosis and treatment of malaria in pregnancy. Additional research priorities are outlined in the panel. The continued use of monotherapies in pregnancy, and general use, requires

Panel: Recommendations for policy and future research

Diagnosis

Policy implementation

- Assess extent to which diagnosis of malaria in pregnancy is done across public and private providers
- Stratify pregnant women into numerator/denominator for parasite-confirmed malaria in Health Medical Information System
- Ensure availability to sensitive diagnostic tests (eg, histidine rich protein 2-based RDTs)

Future research

- Evaluate ultra-sensitive RDTs (Malaria Ag P.f; Alere, Waltham, MA, USA) for detection of malaria infections in pregnancy
- Develop other more sensitive diagnostic tests for all *Plasmodium* species

Treatment of uncomplicated malaria in pregnancy

Policy implementation

- Systematically assess the quality of case management practices of malaria in pregnancy across public and private service providers
- Review pre-service and in-service training curricula for health providers
- Provide quality training, guidelines, and job aids for health providers
- Educate pregnant women on drug safety and side-effects

Future research

- Treat uncomplicated non-*Plasmodium falciparum* malaria, including liver stages

Treatment of severe malaria in pregnancy

Future research

- Treat severe non-*P falciparum* malaria in pregnancy

Pharmacovigilance

Policy implementation

- Start or strengthen national post-marketing surveillance of ACT in all trimesters of pregnancy
- Set up a global pregnancy registry for drug safety including antimalarial drugs (with WHO)

Future research

- Develop cost-efficient pharmacovigilance systems that are suitable for low-income countries (eg, probabilistic record linkage)
- Continue pharmacovigilance for first trimester exposure to antimalarial drugs to better estimate the risk of major congenital malformations

Pharmacokinetics

Future research

- Optimise ACT doses in pregnancy

Drug resistance

Policy implementation

- Monitor drug resistance
- Produce legislation to prevent availability and use of monotherapies

Future research

- Research new alternatives to ACTs given the recent emergence of multidrug resistance

RDT=rapid diagnostic test. ACT=artemisinin-based combination therapy.

For the **Malaria in Pregnancy library** see http://library.mip-consortium.org/

national legislation to prohibit their availability and use. Pregnant women need access to information about which antimalarial drugs are safe.

Additionally, there is a need to establish efficient systems for pharmacovigilance that identify and report possible drug-related safety signals. Such surveillance is particularly difficult in low-income countries because of specific challenges, such as geographical remoteness of many health facilities, poor telecommunication systems, and inadequate education of health professionals and patients.[36,133] The safety of medications during pregnancy could be monitored by different prospective designs, including pregnancy registers, but these require substantial resources that are not readily available in most countries where malaria is endemic. Probabilistic record linkage to assess the risk of major congenital malformations and stillbirth is one possible approach, but medical registers would need to be well maintained.[134] To adequately address these programmatic challenges, improved dialogue and collaboration will be needed between researchers, policy makers, and funders.

Search strategy and selection criteria

We searched PubMed for articles published between Jan 1, 2000, and June 31, 2017 using the terms "pregnan*" AND "malaria". We added additional terms when searching for literature on each specific topic. For diagnosis, we added "diagnostic tests". For treatment efficacy, we added "treatment*" AND "efficacy". For pharmacokinetics, we added "pharmacokinetic*". For safety, we added "safety". For access to treatment, we searched Web of Knowledge, OvidSP, and the Malaria in Pregnancy library for articles published since the most recent review on this topic (Hill and colleagues, 2014) using search terms "pregnan* AND "malaria" AND "treat*" OR "treatment seeking" OR "health seeking" OR "care seeking" OR "provider*" OR "ANC" OR "antenatal" OR "health provider" OR "health-work*" OR "health servic*" OR "drug shop" OR "community health worker" OR "CHW" OR "chemical-seller" OR "ADDO" OR "community drug dispens*" OR "formal" OR "informal" OR "case management" OR "control" OR "management" OR "diagno*" OR "prescrib*" OR "treat*" OR "practice*" OR "chloroquine" OR "CQ" OR "quinine" OR "ACT" OR "artemisinin-based combination therapy" OR "safe*" OR "refer*", AND "utilisation" OR "utilization" OR "coverage" OR "barrier*" OR "attendance" OR "compliance" OR "adherence" OR "attitude*" OR "knowledge" OR "practic*" OR "belie*" OR "perception*" OR "delivery" OR "delivery effectiv*" OR "determinant*" OR "distribut*" OR "evaluat*" OR "delivery system*" OR "predictor" OR "DOT*" OR "directly observed" OR "uptake" OR "behaviour*" OR "behavior*" OR "perception*" OR "accept*" OR "acceptance" OR "availability" OR "awareness" OR "recog*" OR "social" OR "cultur*" OR "socio-cultural" OR "societal". There were no language restrictions.

Contributors

UD-A, JH, and ES conceived the idea for this work. UD-A coordinated the scope and structure of the manuscript. UD-A, JH, JT, and ES drafted individual sections of the manuscript. All authors approved the final version of the manuscript.

Declaration of interests
We declare no competing interests.

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