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Abstract: Over the past 10 years, the available evidence on the treatment of malaria during pregnancy has increased substantially. Considering their relative ease of use, good sensitivity and specificity, histidine rich protein² based rapid diagnostic tests are particularly appropriate for symptomatic pregnant women while they seem less appropriate for systematic screening as they will miss 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 currently being reviewed by the World Health Organization. For the second and third trimester of pregnancy, results from several trials have confirmed that artemisinin-based combination treatments are safe and efficacious, though tolerability and efficacy may vary by treatment. It is now essential to translate such evidence into policies and practice that benefit pregnant women in malaria-endemic countries. Access to parasitological diagnosis and/or appropriate antimalarial treatment in many countries and regions remains low. 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 antimalarials, particularly in the first trimester of pregnancy.

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Abstract (221 words)

Over the past 10 years, the available evidence on the treatment of malaria during pregnancy has increased substantially. Considering their relative ease of use, good sensitivity and specificity, histidine rich protein² based rapid diagnostic tests are particularly appropriate for symptomatic pregnant women while they seem less appropriate for systematic screening as they will miss 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 currently being reviewed by the World Health Organization. For the second and third trimester of pregnancy, results from several trials have confirmed that artemisinin-based combination treatments are safe and efficacious, though tolerability and efficacy may vary by treatment. It is now essential to translate such evidence into policies and practice that benefit pregnant women in malaria-endemic countries. Access to parasitological diagnosis and/or appropriate antimalarial treatment in many countries and regions remains low. 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 antimalarials, particularly in the first trimester of pregnancy.

Introduction

All malaria infections in pregnancy should be treated promptly with safe and efficacious antimalarial drugs to prevent their harmful effects on the mother and foetus (1,2).

Concerns about the potential for harm of new antimalarial treatments on pregnant women or their unborn baby has led to their systematic exclusion from clinical trials, resulting in limited information on 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 (www.mip-consortium.org) and others, addressing knowledge gaps, and herein we present a summary of the results.

Search strategy

Four separate systematic reviews were conducted, one for each of the major topic areas: diagnosis, efficacy, pharmacokinetics, safety, and access to treatment. Their respective search strategies are outlined in the supplemental appendix and results are provided below.

Diagnosis

Case management of malaria consists of identifying a suspect case, based on the presence of signs/symptoms, and performing diagnostic testing followed by treatment if needed. The accuracy of diagnostic tests depends on parasite density. Microscopy with an experienced and well equipped microscopist has a detection threshold of 15 parasites per μL of blood (1) while for rapid diagnostic tests (RDT), which detect circulating parasite antigens, this may be as low as 200 parasites per μL (9). Such diagnostic tests (microscopy and RDTs) may be adequate for pregnant women with malaria symptoms as they usually have parasite densities above their detection thresholds (10). Nevertheless, the large majority of infections during pregnancy are asymptomatic, with low parasite densities, often not detected by microscopy. The public health importance of such infections is controversial as they have been associated with anaemia, lower mean Hb, low birth weight, and

premature births in some studies (11) but not in others (12). Intermittent screening and treatment, a potential alternative to intermittent preventive treatment with sulfadoxine-pyrimethamine (SP) in places of high SP resistance or low malaria transmission, is based on the assumption that currently available tests, more specifically RDTs, should be able to identify most infections. This is probably not the case though, thanks to their ability to detect circulating parasite antigens, RDTs may be useful in diagnosing placenta malaria, particularly for *P. 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 94% [95% CI 76-99], while polymerase chain reaction (PCR) had higher sensitivity (94%, 95% CI 86-98) but lower specificity (77%, 95% CI 71-82) (14). However, in Papua New Guinea, more than half of active placenta infections were not diagnosed by RDT, microscopy, or PCR on 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 and specificity on peripheral blood for diagnosing placenta malaria was 92.7% and 91.8%, respectively (17). As for peripheral infections, RDTs had similar (18,19) or lower (10) sensitivity than microscopy, with histidine rich protein2 (HRP2)-based RDT performing better than plasmodium lactate dehydrogenase (pLDH)-based RDTs (10,20).

Considering their relative ease of use, good sensitivity and specificity, HRP2-based RDTs are particularly appropriate for symptomatic pregnant women while they are less appropriate for systematic screening as they will miss an important proportion of infections among asymptomatic pregnant women. The newly available ultra-sensitive RDT (Alere™ Malaria Ag P.f) should be evaluated for detecting low-density infections in pregnant women.

Treatment of uncomplicated malaria

First trimester

For *P. falciparum* malaria during the first trimester, the WHO recommends quinine with clindamycin for seven days (or quinine alone if clindamycin is not available) and, in case of failure or unavailability, an artemisinin-based combination therapy (ACT) or oral artesunate with clindamycin for seven days (2). This is based on data from 700 pregnant women exposed to artemisinin derivatives during the first trimester, and excludes a ≥ 4.2 -fold increase in risk of major congenital defects (2). However, the Malaria Policy Advisory Committee recommended recently revising these guidelines on the basis of a recent meta-analysis (21,22).

Non-falciparum malaria should be treated with chloroquine; in case of chloroquine-resistant infections, quinine is recommended (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, i.e. any ACT recommended as national first-line treatment, namely artemether-lumefantrine, artesunate-amodiaquine, artesunate-mefloquine, dihydroartemisinin-piperaquine, or artesunate plus sulfadoxine-pyrimethamine (2). A systematic review including 16 randomized control trials done between 1998 and 2009 (23) presented ten trials testing ACTs (three artesunate plus sulfadoxine-pyrimethamine, two artemether-lumefantrine, three artesunate-mefloquine, one dihydroartemisinin-piperaquine and one artesunate with atovaquone-proguanil) versus either combinations without artemisinins or monotherapies. In most trials, ACTs had a PCR-adjusted efficacy >90%, with the exception of artemether-lumefantrine at the Thai-Burmese border with an efficacy of 87% at day 42 (23), 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 antimalarials (azithromycin plus SP; SP plus amodiaquine) included 6 trials done between 1995 and 2009, three from sub-Saharan Africa (Malawi, Tanzania, Uganda) and three from Asia (Thailand), all of them included in the previous

review (23), except the one in Uganda (25). ACTs were significantly more efficacious than oral quinine, had similar efficacy to non-ACTs in Africa and significantly higher efficacy in Thailand. Birth outcomes were similar between treatment arms, with the exception of mean birth weight that was significantly higher in ACT versus non-ACT recipients, indicating ACTs may clear parasites, including those in the placenta, more efficiently than other treatments (26). Furthermore, artemether-lumefantrine was associated with decreased rates of moderate to high-grade haemozoin deposition in the placenta (13.3% versus 25.8%) compared to oral quinine in Uganda, indicating a protective effect against placental malaria (27).

A large multicentre randomized open-label trial testing four ACTs (artemether-lumefantrine, artesunate-amodiaquine, artesunate-mefloquine, and dihydroartemisinin-piperaquine) in pregnant women with *P. falciparum* malaria was carried out between 2010 and 2013 in four sub-Saharan African countries (Burkina Faso, Ghana, Malawi, and Zambia). A total of 3,428 pregnant women were recruited and followed up until day 63 post-treatment and then at delivery. The PCR-adjusted cure rates for all ACTs ranged from 94.8% to 99.2%, within the pre-specified 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%) indicate that in areas of intense transmission dihydroartemisinin-piperaquine may be preferable to artemether-lumefantrine because of its longer post-treatment prophylactic period.

Recently, a few smaller trials carried out in sub-Saharan Africa (Nigeria (29) and Uganda(30)) confirmed the high efficacy of ACTs.

In southern Papua New Guinea, Indonesia, dihydroartemisinin-piperaquine became the first line treatment for second and third trimester pregnant women in 2006, and this resulted in a decline of congenital malaria cases, from 3.2% to 0.2%, with no case detected since 2008 (31). The implementation of dihydroartemisinin-piperaquine also resulted in a lower risk of malaria at delivery, early neonatal deaths (32), maternal severe anaemia, and low birth weight (33).

Though chloroquine can be used for treating non-falciparum malaria (1), *P. vivax* resistance emerged in the 1980s in New Guinea and has spread to the Indonesian archipelago and Mekong region (34). Almost all antimalarial drugs with activity against *P. falciparum* demonstrate intrinsic activity against *P. vivax* asexual stages, with the exception of antifolate drugs (34). Therefore, *vivax* malaria can be treated with any ACT effective against *P. falciparum*, with the exception of artesunate plus sulfadoxine-pyrimethamine (2). ACTs rapidly clear *P. vivax* asexual stages though there is high variability in the occurrence of recurrent infection between 28 and 63 days post-treatment (34). Unfortunately, primaquine, the only available drug effective against the parasite's liver stages, is contraindicated in pregnancy and breast feeding, due to the risk of haemolysis if the offspring is glucose-6-phosphate dehydrogenase deficient (34); it 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 low transmission settings, where it is often complicated by pulmonary oedema and hypoglycaemia (2). Intensive care and prompt parenteral antimalarial treatment are critical to the mother's survival (1). A recent review on the treatment of severe malaria in all trimesters of pregnancy identified ten studies that reported clinical outcomes (35). The review supports WHO recommendation for intravenous artesunate as the drug of choice, or if unavailable, intramuscular artemether (2), though for the latter the absorption is less predictable, especially in patients with cardiovascular collapse

(1). Parenteral quinine, though associated with recurrent hypoglycaemia, can be used when artesunate or artemether are not available (2).

Until controlled clinical trials are conducted, severe non-falciparum malaria should be managed as severe falciparum malaria in intensive care settings with intravenous artesunate or quinine (34).

Pharmacokinetics (Table 1)

Pregnancy is associated with a number of physiological changes that can alter drug absorption, disposition, metabolism and excretion (36). It is therefore imperative to recognize pregnancy-related changes in pharmacokinetic properties since these may result in over- or under-exposure to antimalarials. Over-exposure might lead to maternal and foetal toxicity and under-exposure to therapeutic failures, resulting in poor pregnancy outcomes, maternal death, and increased risk of drug resistance (36,37). The current literature on the pharmacokinetic of antimalarials in pregnancy is often contradictory and based on small studies without non-pregnant control patients. Controlled prospective pharmacokinetic studies are needed to evaluate the pregnancy effect. Ideally, non-pregnant controls should be matched by sex, malaria infection status, and age to control for confounding covariates, and evaluated with pharmacokinetic modelling approaches to quantify potential pregnancy-specific effects.

Artemisinin

Systemic drug exposure to artesunate and its active metabolite dihydroartemisinin, following oral administration of artesunate, was substantially lower in pregnant women with 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 were shown to have 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 alteration on 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 Congo, comparing women during pregnancy and post-partum with non-pregnant controls confirmed an altered drug exposure in pregnant women (42% decreased exposure to dihydroartemisinin) after oral administration of artesunate (41,42). However, no difference was seen in the exposure to dihydroartemisinin in pregnant and non-pregnant women in Burkina Faso after oral artesunate treatment (43).

The pharmacokinetic properties of artemether and its active metabolite dihydroartemisinin, after oral administration of artemether, are reported to be unaltered in two clinical studies in pregnant women and matched non-pregnant controls in Uganda and Tanzania (30,44). However, studies recruiting only pregnant women have reported lower drug exposures in pregnant women compared to historical controls (45–48).

Contradictory results have also been presented regarding the systemic drug exposure to dihydroartemisinin, following oral administration in pregnant women and matched non-pregnant controls (49–52). In Thailand and Uganda, drug exposure was substantially lower (38% and 47%, respectively) in pregnant women (50) while in Papua New Guinea pharmacokinetic properties in pregnant women were unaltered (49).

Thus, ACTs may need a dose adjustment (higher dose) but more information is needed. A recently-published systematic review reached similar conclusions (53).

4-amino-quinolines

Drug exposure to chloroquine and its main metabolite desethylchloroquine was significantly reduced (25% and 45%, respectively) in pregnant women compared to age-matched non-pregnant women in Papua New Guinea when receiving three daily doses (450 mg/day) of chloroquine as intermittent preventive treatment (54). This was due to increased elimination of both chloroquine and desethylchloroquine during pregnancy. However, pharmacokinetic parameters of chloroquine or desethylchloroquine were not different between pregnant and non-pregnant Karen women with vivax malaria (55).

No differences in the pharmacokinetic properties of amodiaquine or desethylamodiaquine were found between pregnant women in the second and third trimesters with vivax malaria and the same women 3 months post-partum (56). Population pharmacokinetic modelling confirmed that pregnancy did not have a clinically relevant impact on the pharmacokinetics of amodiaquine or desethylamodiaquine, with no need of dose adjustment (57).

Contradictory results have been presented 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 falciparum malaria in Thailand (51). Population pharmacokinetic modelling 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 (50). Similar results were obtained in pregnant and age- and weight-matched non-pregnant Sudanese women with falciparum malaria (58,59). However, an approximately 40% lower exposure to piperaquine in pregnant than non-pregnant women has been reported in Papua New Guinea and Uganda (49,52).

Quinoline methanols and related drugs

No relevant differences were found in the exposure to mefloquine between pregnant women in their second and third trimester and matched non-pregnant women with falciparum malaria in Burkina Faso when treated with artesunate-mefloquine (43). However, peak mefloquine concentrations were significantly lower in pregnant than non-pregnant women with falciparum malaria compared with treated with a single oral dose of mefloquine (60). Similarly, a dose finding study on the Thai-Myanmar border suggests that drug exposure to mefloquine may be decreased in late pregnancy (61).

Mean pharmacokinetic parameters of quinine and its metabolites were not significantly different between Sudanese pregnant and non-pregnant women with *falciparum* malaria who received a single dose of quinine hydrochloride (as intravenous infusion over 2 hours), suggesting that no dose adjustment is required in pregnancy (62). However, in these women exposure to quinine during clinical malaria was higher than during the convalescence phase (63). A higher exposure to quinine during clinical malaria as compared to the convalescence phase was similarly reported in Ugandan pregnant women with falciparum malaria and treated with oral quinine. However, drug exposure was about half of those previously reported in non-pregnant patients (36).

The systemic drug exposure to lumefantrine is generally reported to be lower in pregnant than non-pregnant women treated with artemether-lumefantrine for falciparum malaria (44,64,65). These studies demonstrate about 30% decrease in day seven concentrations of lumefantrine in pregnant versus non-pregnant patients. However, one study in rural Uganda reported no differences in the exposure to lumefantrine between pregnant women and non-pregnant women with falciparum malaria (30).

Antifolates

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

Drug safety (Table 2)

Firm conclusions on the safety of antimalarial drugs in pregnancy are limited by methodological issues. Studies are often underpowered to detect rare safety outcomes and small differences. The trial design often covers a short/sporadic follow-up period (69) and lack statistical power to adjust for uncontrolled confounders like severity of disease and/or presence of sexually transmitted infections, 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 (70). In humans, dihydroartemisinin is responsible for the erythro-toxicity (71,72). In rats, gestational days 10 to 14 were the most sensitive to the embryo-lethal effects of artesunate; the corresponding gestational age in humans is approximately week three to week nine post-conception (73). Artemisinins concentrate in infected red blood cells while malaria causes hypoferrremia (74). Therefore, malaria may protect against artemisinin-induced decreases in reticulocyte count by reducing the target tissue levels of active drug and/or ferrous iron which activates the drug to toxic-

free radicals; malaria protection against artesunate toxicity has been observed in rats. This could be true also for embryotoxicity so that pregnant women without malaria would be at greater risk of artemisinin-induced embryotoxicity (73).

A meta-analysis on 1,664 well-documented pregnancies followed after artemisinin or quinine treatment during the first trimester reported no differences in the risk of miscarriage, stillbirth, or major congenital malformations between artemisinins and quinine (22). Risk of miscarriage was similar between women treated with artemisinins during the first trimester and those not treated with an antimalarial; the risk was significantly higher for women treated with quinine than in those not treated with an antimalarial (22,75). In Thailand, the risk of miscarriage among women attending antenatal clinics during the years 1986-2010 was not significantly different in those treated between six and 12 weeks of gestation with artesunate (31%), quinine (27%) or chloroquine (26%) ($p=0.71$) (76). The risk of miscarriage associated with malaria outweighed any adverse effects from treatment with antimalarials, including artemisinins (76).

In Thailand, first trimester pregnant women exposed to either artemisinins ($n=183$) or quinine ($n=971$) had a similar risk of miscarriage. Considering only exposure during the embryo-sensitive window (6-13 weeks gestation), the occurrence of congenital malformations for artemisinins or quinine was similar although the sample size was small (77). In Kenya (78), Tanzania (79), Zambia (80), and Rwanda (81), first trimester exposure was reported in 299, 319, 294, and 96 pregnant women, respectively. In Kenya, the risk of miscarriage tended to be higher among women treated with artemisinins compared to women with no exposure to antimalarial drugs, though this did not apply when considering only exposure during the embryo-sensitive period or when comparing to women treated with quinine. In Tanzania, adverse pregnancy outcomes (miscarriage/stillbirth, prematurity) were more common in women treated with quinine than with any other antimalarial, including artemether-lumefantrine. In Zambia, first trimester exposure to antimalarials was not associated with adverse pregnancy outcomes (80).

Artemether-lumefantrine in the first trimester of pregnancy did not increase the risk of perinatal or neonatal death or stillbirth. Infant neurodevelopment, birth weight, and the overall incidence of birth defects were also similar, irrespective of treatment with artemether-lumefantrine or other antimalarials during the first trimester. All cases of miscarriage in the artemether-lumefantrine exposure group occurred in patients who had received treatment during the first trimester, although in most cases there were confounding factors (82). 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 of second and third trimester exposure to ACTs in studies in Africa and Asia indicates that the risk of miscarriage and congenital anomalies is similar among women in second or third trimester of pregnancy treated with artemisinins and women treated with quinine or other non-artemisinin antimalarials. This meta-analysis also reported that the risk of stillbirth was lower in ACT compared to quinine recipients, possibly reflecting a higher efficacy of artemisinins treatment (83).

In the second and third trimester, artemether-lumefantrine (n=903) was not associated with increased adverse pregnancy outcomes as compared with quinine (n=152) or sulfadoxine-pyrimethamine (n=378), showed improved tolerability relative to quinine, and its efficacy was non-inferior to quinine (84).

Between 1948 and 1990, only six published studies reported amodiaquine use in pregnancy, and only one publication mentioned adverse events but with limited information (85). More recently, amodiaquine alone or in combination with sulfadoxine-pyrimethamine during the second or third

trimester was not associated with liver toxicity or bone marrow depression (86). In Ghana, women treated with amodiaquine alone or combined with sulfadoxine-pyrimethamine reported a higher frequency of mild adverse events but no difference in miscarriages, stillbirths, neonatal jaundice, and neonatal deaths (87). At standard dosages, amodiaquine is not teratogenic and the adverse events observed during pregnancy are no greater than those associated with falciparum malaria in pregnancy (88). More recent but smaller studies reported amodiaquine to be safe and reasonably well tolerated (56). Amodiaquine-artesunate was not associated with adverse birth outcomes (89). Similarly, the proportion of women who reported adverse events during the seven days following treatment did not differ significantly between treatment groups (IPTp-SP, and treatment with SP or amodiaquine-artesunate) with the exception of general weakness, which was reported slightly more frequently in women treated with amodiaquine-artesunate (90).

Dihydroartemisinin-piperaquine was well tolerated and had an acceptable safety profile in one arm of a recent trial with more than 800 African pregnant women treated in the second and third trimester (28). These results confirm other smaller studies carried out in Asia (51,91) and Africa (58,59). Although dihydroartemisinin-piperaquine can cause prolongation of the QT interval (92), no clinically significant prolongation of the QT interval was seen on 42 pregnant women receiving dihydroartemisinin-piperaquine (93,94).

Initial concerns on the association between mefloquine and stillbirth arose as a result of a retrospective analysis in Thailand (95). This finding was not supported by earlier studies evaluating mefloquine for treatment of malaria in pregnancy, nor by later studies on mefloquine-artesunate (96–98). Birth defect prevalence and foetal loss were comparable with background rates in 2,506 pregnant women exposed to mefloquine (99). Mefloquine-artesunate was less well tolerated than artemether-lumefantrine and dihydroartemisinin-piperaquine, and drug-related adverse events were more frequent in 850 African women in the second and third trimester of pregnancy with

falciparum malaria; pregnancy outcomes were similar to other antimalarial treatments (28). When mefloquine alone was used as intermittent preventive treatment, incidence of spontaneous abortions, stillbirths, and congenital anomalies did not differ significantly with the sulfadoxine-pyrimethamine groups, though adverse events were more frequent (100). Adverse events were common, though mostly minor, in 103 HIV-infected and 421 HIV-negative Beninese pregnant women to whom mefloquine was administered as intermittent preventive treatment. Interestingly, mefloquine tolerability was better in HIV-infected women, a finding possibly explained by these women being more familiar with experiencing adverse events and thus less prone to report them systematically (101). In two recent studies for prevention of malaria in African HIV positive and negative women, mefloquine was less well-tolerated than sulfadoxine-pyrimethamine (102,103). In the HIV positive women study, the viral load and the frequency of mother to child transmission of HIV was higher in the mefloquine group but this result needs to be confirmed (104).

Sulfadoxine-pyrimethamine has been used extensively in pregnancy for treatment and intermittent preventive treatment, but formal safety studies are limited (36). Pyrimethamine causes dose-dependent embryotoxicity in rats, but not at human-equivalent doses (105). In a case-control study, mothers whose babies had cleft palate had had a higher exposure to sulfonamide than controls (105). Nevertheless, although folate antagonist use in the first trimester is associated with neural tube defects, large case-control studies have demonstrated that sulfadoxine-pyrimethamine administered as IPTp does not increase the risk of teratogenesis (106). In Malawi (107) and Sudan (108), sulfadoxine-pyrimethamine associated with artesunate administered to pregnant women with falciparum malaria seemed safe and well tolerated, though the sample size in both countries was small. Similarly, in The Gambia, exposure to sulfadoxine-pyrimethamine and a single dose of artesunate administered to pregnant women in the context of a mass drug administration exercise did not report any teratogenic or other harmful effect (109). Sulfadoxine-pyrimethamine should not be administered concurrently with cotrimoxazole given their redundant mechanisms of action and

synergistic worsening of adverse drug reactions (110). No clinical association between sulfadoxine-pyrimethamine and kernicterus has been reported (106).

Quinine

The use of quinine in pregnancy is generally thought to be safe, and it is not associated with poor birth outcomes (36). Quinine has been shown to cause prolongation of the QT interval, but no significant cardiotoxicity has been reported in large prospective studies (111). 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 in the artemether-lumefantrine arm (25).

Chloroquine

Chloroquine has been described as safe throughout pregnancy (112). However, chloroquine has been shown to cause prolongation of the QT interval but with no significant cardiotoxicity reported in large prospective studies (111). A study in Thailand reported that the risk of miscarriage was similar for women treated with chloroquine, quinine, or artesunate (76).

Access to treatment

Despite wide-scale adoption of the 2006 WHO recommendations (113) to use ACTs to treat uncomplicated malaria in the second and third trimester of pregnancy, access to parasitological diagnosis and/or appropriate antimalarial treatment in many countries and regions remains low. In a systematic review of women's access and provider practices, case management practices among healthcare providers in the public, private, and retail sectors were generally poor (114). Reliance on clinical diagnosis and poor adherence to treatment policy was consistently reported across different cadres and settings (114). Adherence to treatment policy in the first trimester of pregnancy was

significantly lower (28%) than in other trimesters (72%) (114). ACTs, which are currently contraindicated in the first trimester (22,113), were prescribed extensively either alongside quinine (recommended policy) (114–117) or exclusively (118). In western Kenya, correct prescription was observed in only 24% of first trimester women exiting health facilities and 0% of simulated clients attending drug outlets, compared to 65% and 40% in other trimesters, respectively. Notably, 49% of first trimester women presenting to drug outlets were prescribed artemether-lumefantrine (116). Drugs no longer recommended for treatment of falciparum malaria in Africa were widely prescribed for all trimesters, including sulfadoxine-pyrimethamine (restricted for use as IPTp/prevention only) in Nigeria (115,117–119) and Kenya (116), and chloroquine in Nigeria (115,117,119). Use of artemether and artesunate monotherapies were widely reported in Nigeria (115,117–119) and in Uganda (120).

Correct treatment practices among health providers were associated with knowledge (119,120), training (114,116), availability of guidelines (120), and facility type (public versus private/drug shops) (114,116). Prescribing practices were driven by concerns over drug side effects and safety, drug availability, patient preference, and cost (114). 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 ensure both the diagnostic tools and the recommended treatments are available at all levels of the health system. Evidence for quality improvement initiatives targeting public and private providers are also needed, alongside legislation to regulate which antimalarials are licenced for sale.

Although pregnant women often report bouts of malaria, anthropological research has highlighted how their understandings of malaria symptoms overlap only partially with biomedical definitions and can be difficult to distinguish from pregnancy-related symptoms (121–124). Such confusion, for example, contributed to delayed treatment seeking in Mali and Kenya (125). Women's choice of healthcare provider was influenced by severity and duration of malaria episode (121,126),

knowledge and perceptions of drug safety, drug availability, and cost and perceptions of healthcare services (114,125), with the use of non-biomedical remedies– homemade or from a local healer – reported in Mali (125), Nigeria (127), South Sudan (126), India (128), and Papua New Guinea (129). Social relationships influenced treatment seeking and some, particularly younger women, sought advice/assistance from relatives (121,124). Observations of self-treatment – prompted by drug or diagnostic costs, irregular drug supplies at health facilities, and/or previous poor quality care – highlight the need for comprehensible advice on antimalarials and dosages that are safe during pregnancy to be made widely available (121).

Perspectives and conclusions

Over the last 10 years, the Malaria in Pregnancy Consortium and other research groups have carried out extensive research to improve the control of malaria in pregnancy, focussing on previously identified priorities (130). Evidence on the treatment of malaria during pregnancy has increased substantially. Malaria in pregnancy can be adequately diagnosed by HRP2-based RDTs; it has been confirmed that available ACTs can be used for the treatment of malaria during the second and third trimester of pregnancy; and the WHO may revise the guidelines on the use of artemisinins in the first trimester of pregnancy. It is now essential to translate this evidence into policies. However, poor quality service provision across public, private, and retail sectors in most endemic regions indicates a pressing need for research to identify quality improvement interventions targeting users and providers. The priorities for policy implementation include health provider training on national policy guidelines for diagnosis and treatment of malaria in pregnancy. The continued use of monotherapies in pregnancy and more generally requires national legislation to prohibit their availability and use. Pregnant women need access to information about which antimalarials are safe.

In addition, there is a need to establish efficient systems for pharmacovigilance able to identify and report possible drug-related safety signals. This is particularly problematic in low income countries because of specific challenges such as geographical remoteness of many of the health facilities, poor telecommunication systems, and inadequate education of health professionals and patients

(36,131). Safety of medications during pregnancy could be monitored by different prospective designs, including pregnancy registers, but these require substantial resources, not readily available in malaria-endemic countries. Probabilistic record linkage to assess the risk of major congenital malformations and stillbirth could be a possible approach but needs well-kept medical registers (132). Adequately addressing these programmatic challenges will require improved dialogue and collaboration between researchers, policy makers and funders. Additional research priorities are outlined in Table 3.

Author Contributions

UDA, JH and ES conceived the concept. UDA coordinated the manuscript scope and structure. UDA, JH, JT and ES drafted individual sections of the manuscript, with critical review of content from all authors. All authors approved the final version of the manuscript.

Conflict of Interest

We declare that we have no conflicts of interest.

Disclaimer

The findings and conclusions presented in this manuscript are those of the authors and do not necessarily reflect the official position of the U.S. Centers for Disease Control and Prevention.

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Table 1

Table 1. Pharmacokinetic summary

Antimalarial	Study patients	Country	Pregnancy effects	Ref
Artesunate	Pregnant women (n = 24)	Thailand	Decreased exposure to dihydroartemisinin in pregnant women compared to historical controls.	38
	Pregnant and post-partum women (n = 20/15)	Thailand	23% decreased exposure to dihydroartemisinin in pregnant women compared to post-partum women.	39, 40
	Pregnant, post-partum and non-pregnant women (n = 26/26/25)	DRC	42% decreased exposure to dihydroartemisinin in pregnant women compared non-pregnant women.	41, 42
	Pregnant and non-pregnant women (n = 24/24)	Burkina Faso	No difference in exposure to dihydroartemisinin in pregnant women compared non-pregnant women.	43
	Contradictory results; generally lower exposure reported in pregnant women.			
Artemether	Pregnant and non-pregnant women (n = 30/30)	Uganda	No difference in exposure to dihydroartemisinin in pregnant women compared non-pregnant women.	44
	Pregnant and non-pregnant women (n = 33/22)	Tanzania	No difference in exposure to dihydroartemisinin in pregnant women compared non-pregnant women.	45
	Pregnant women (n = 21)	Uganda	Decreased exposure to dihydroartemisinin in pregnant women compared to historical controls.	45, 48
	Pregnant women (n = 13)	Thailand	Decreased exposure to dihydroartemisinin in pregnant women compared to historical controls.	47
	Contradictory results; generally no difference in exposure reported in pregnant women.			
Dihydroartemisinin	Pregnant and non-pregnant women (n = 32/33)	Papua New Guinea	No difference in exposure to dihydroartemisinin in pregnant women compared non-pregnant women.	49
	Pregnant and non-pregnant women (n = 24/24)	Thailand	38% decreased exposure to dihydroartemisinin in pregnant women compared non-pregnant women.	50, 51
	Pregnant and non-pregnant women (n = 31/30)	Uganda	47% decreased exposure to dihydroartemisinin in pregnant women compared non-pregnant women.	52
	Contradictory results; no difference and decreased exposure reported in pregnant women.			
Chloroquine	Pregnant and non-pregnant women (n = 30/30)	Papua New Guinea	34% decreased exposure to chloroquine in pregnant women compared non-pregnant women.	54
	Pregnant and non-	Thailand	No difference in exposure to chloroquine in	55

	pregnant women (n = 12/15)		pregnant women compared non-pregnant women.	
	Pregnant women (n = 49)	Tanzania	Decreased exposure to chloroquine in pregnant women compared to historical controls.	133
Contradictory results; no difference and decreased exposure reported in pregnant women.				
Amodiaquine	Pregnant and post-partum women (n = 24/18)	Thailand	No difference in exposure to amodiaquine and desethylamodiaquine in pregnant women compared to post-partum women.	56, 57
	No difference in exposure reported in pregnant women.			
Piperaquine	Pregnant and non-pregnant women (n = 32/33)	Papua New Guinea	42% decreased exposure to piperaquine in pregnant women compared non-pregnant women.	49
	Pregnant and non-pregnant women (n = 24/24)	Thailand	No difference in exposure to piperaquine in pregnant women compared non-pregnant women.	50, 51
	Pregnant and non-pregnant women (n = 12/12)	Sudan	No difference in exposure to piperaquine in pregnant women compared non-pregnant women.	58, 59
	Pregnant and non-pregnant women (n = 31/30)	Uganda	40% decreased exposure to piperaquine in pregnant women compared non-pregnant women.	52
	Contradictory results; no difference and decreased exposure reported in pregnant women.			
Mefloquine	Pregnant and non-pregnant women (n = 24/24)	Burkina Faso	No difference in exposure to mefloquine in pregnant women compared non-pregnant women.	43
	Pregnant and non-pregnant women (n = 9/8)	Burkina Faso	No difference in exposure to mefloquine in pregnant women compared non-pregnant women.	60
	Pregnant women (n = 20)	Thailand	Decreased exposure to mefloquine in pregnant women compared to historical controls.	61
	Contradictory results; generally no difference in exposure reported in pregnant women.			
Quinine	Pregnant women (n = 22)	Uganda	Decreased exposure to quinine in pregnant women compared to historical controls.	45, 46
	Pregnant and non-pregnant women (n = 8/8)	Sudan	No difference in exposure to quinine in pregnant women compared non-pregnant women.	62
	Pregnant and non-pregnant women (n = 9/8)	Sudan	No difference in exposure to quinine in pregnant women compared non-pregnant women.	63
	Contradictory results; generally no difference in exposure reported in pregnant women.			
Lumefantrine	Pregnant and non-pregnant women (n	Uganda	No difference in exposure to lumefantrine in pregnant women compared non-pregnant	39

	= 30/30)		women.	
	Pregnant and non-pregnant women (n = 33/22)	Tanzania	34% decreased exposure to lumefantrine in pregnant women compared non-pregnant women.	44
	Pregnant and non-pregnant women (n = 26/17)	Uganda	No difference in exposure to lumefantrine in pregnant women compared non-pregnant women.	45
	Pregnant women (n = 13)	Thailand	Decreased exposure to lumefantrine in pregnant women compared to historical controls.	47
	Pregnant and non-pregnant women (n = 116/17)	Uganda	No difference in exposure to lumefantrine in pregnant women compared non-pregnant women.	64
	Pregnant women (n = 103)	Thailand	Decreased exposure to lumefantrine in pregnant women compared to historical controls.	65
	Contradictory results; generally no difference in exposure reported in pregnant women.			
Sulfadoxine	Pregnant and non-pregnant women (n = 30/30)	Papua New Guinea	33% decreased exposure to sulfadoxine in pregnant women compared non-pregnant women.	66
	Pregnant and post-partum women (n = 33/11)	Kenya	43% decreased exposure to sulfadoxine in pregnant women compared to post-partum women.	67
	Pregnant and post-partum women (n = 43/40)	Mali, Zambia	No difference in exposure to sulfadoxine in pregnant women compared to post-partum women.	68
	Pregnant and non-pregnant women (n = 87/34)	Uganda	82% decreased exposure to sulfadoxine in pregnant women compared non-pregnant women.	134
	Contradictory results; generally decreased exposure reported in pregnant women.			
Pyrimethamine	Pregnant and non-pregnant women (n = 30/30)	Papua New Guinea	32% decreased exposure to pyrimethamine in pregnant women compared non-pregnant women.	66
	Pregnant and post-partum women (n = 33/11)	Kenya	No difference in exposure to pyrimethamine in pregnant women compared to post-partum women.	67
	Pregnant and post-partum women (n = 43/40)	Mali, Zambia	31% increased exposure to pyrimethamine in pregnant women compared to post-partum women.	68
	Pregnant and non-pregnant women (n = 87/34)	Uganda	34% decreased exposure to pyrimethamine in pregnant women compared non-pregnant women.	134
	Contradictory results; no difference, increased and decreased exposure reported in pregnant women.			

Relative difference in exposure calculated as $(AUC_{\text{comparison}} - AUC_{\text{pregnancy}}) / AUC_{\text{comparison}}$.

Table 2: Summary of antimalarials safety profile

Drugs	Safety profile	References
Artemisinin derivatives and partner drugs	<ul style="list-style-type: none"> • 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. • Amodiaquine-artesunate has been associated with general weakness, vomiting, dizziness, and nausea but without increased risk of miscarriage, stillbirth, or major congenital malformations. • Dihydroartemisinin-piperaquine is well tolerated. Concerns regarding prolongation of the QT interval were raised. More studies are needed to understand the clinical significance of this event in pregnant women. • Mefloquine-artesunate was less well tolerated when compare with other combinations (artemether-lumefantrine, dihydroartemisinin-piperaquine). • Sulfadoxine-pyrimethamine - artesunate seemed safe and well tolerated. 	22, 71, 72, 73, 77, 83, 85, 89, 91, 93, 94, 107, 109.
Mefloquine	<ul style="list-style-type: none"> • 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 	95, 96, 97, 98, 99, 101, 103, 104, 108, 112.

	<p>abortions, stillbirths, and congenital anomalies did not differ significantly compared to sulfadoxine-pyrimethamine.</p>	
Sulfadoxine-pyrimethamine	<ul style="list-style-type: none"> • Sulfadoxine-pyrimethamine should not be administered concurrently with cotrimoxazole given their redundant mechanisms of action and synergistic worsening of adverse drug reactions particularly cutaneous reactions. • Was reported to be associated with neural tube defects when used in first trimester, but when administered as IPTp in the second and third trimesters does not result in an increased risk of teratogenesis. 	86, 87, 106, 110.
Quinine	<ul style="list-style-type: none"> • Quinine is less well tolerated when comparing with other antimalarials and can cause hypoglycaemia and tinnitus, particularly in the second and third trimester. Prolongation of the QT interval with no significant cardiotoxicity has been reported. 	105, 111.
Chloroquine	<ul style="list-style-type: none"> • Chloroquine has been described as safe throughout pregnancy. • The risk of miscarriage was similar for women treated with chloroquine, quinine, or artesunate. 	105, 112.

Table 3. Recommendations for policy and future research

Topic/programme area	Policy implementation	Future research
Diagnosis	<ul style="list-style-type: none"> – Assess extent to which diagnosis of malaria in pregnancy is practiced across public and private providers – Stratify pregnant women in numerator/denominator for parasite confirmed malaria in HMIS – Ensure availability to sensitive diagnostic tests e.g. HRP2-based RDTs 	<ul style="list-style-type: none"> – Evaluate ultra-sensitive RDT (Alere™ Malaria Ag P.f) for detection of infections in pregnancy – Develop other more sensitive diagnostic tests for all Plasmodium species
Treatment of uncomplicated malaria in pregnancy	<ul style="list-style-type: none"> – Systematic assessment of the quality of case management of MiP practices across public and private service providers – Review pre-service and in-service training curriculae – Provide quality training, guidelines, and job aids for health providers – Education of pregnant women on drug safety and side effects in pregnancy 	<ul style="list-style-type: none"> – Treatment of uncomplicated non-falciparum malaria, including treatment of liver stages
Treatment of severe malaria in pregnancy		<ul style="list-style-type: none"> – Treatment of severe non-falciparum malaria in pregnancy
Pharmacovigilance	<ul style="list-style-type: none"> – National post marketing surveillance of ACTs in all trimesters of pregnancy – Global pregnancy registry for drug safety including antimalarials (WHO) 	<ul style="list-style-type: none"> – Develop cost-efficient pharmacovigilance systems suitable for low income countries e.g. probabilistic record linkage – Continued pharmacovigilance for first trimester exposure to antimalarials to better estimate the risk of major congenital malformations
Pharmacokinetics		<ul style="list-style-type: none"> – Optimization of ACT dosages in pregnancy
Drug resistance	<ul style="list-style-type: none"> – Drug resistance surveillance monitoring – Legislation to prevent availability and use of monotherapies 	<ul style="list-style-type: none"> – New treatment alternatives to ACTs given the recent emergence of multidrug resistance