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Artemisinin-Based Combination Therapy Compared to Chloroquine for Malaria Clearance in Pregnant Women: A Comparative Effectiveness Review

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ABSTRACT

Malaria in pregnancy poses a major public health threat due to increased maternal susceptibility and the risk of adverse fetal outcomes. Effective antimalarial therapy is essential to mitigate complications such as maternal anemia, intrauterine growth restriction, and stillbirth. Chloroquine, once the cornerstone of malaria treatment, has lost efficacy in many regions due to widespread resistance. In response, artemisinin-based combination therapies (ACTs) have emerged as the preferred treatment option, offering rapid parasite clearance and reduced recrudescence. This comparative effectiveness review synthesized findings from randomized controlled trials, observational studies, and pharmacovigilance reports to evaluate the relative performance of ACTs and chloroquine in pregnant women. A narrative review methodology was employed to systematically integrate clinical evidence and contextual health system factors. Evidence indicates that ACTs outperform chloroquine in parasitemia clearance and maternal and neonatal outcomes, especially in regions with high chloroquine resistance. While chloroquine remains a safe and cost-effective option in sensitive regions, its declining utility highlights the need for treatment strategies informed by local resistance profiles. ACTs demonstrate favorable safety in the second and third trimesters, supporting their integration into antenatal care protocols. Region-specific policies, pharmacovigilance, and health system support are essential to optimize malaria treatment and reduce pregnancy-related complications in endemic areas.

Keywords: Malaria in pregnancy, Artemisinin-based combination therapy (ACT), Chloroquine resistance, Parasite clearance, Maternal and neonatal outcomes.

INTRODUCTION

Malaria during pregnancy represents a critical public health challenge, particularly in endemic regions where Plasmodium falciparum transmission is intense and persistent [1–3]. Pregnant women are significantly more susceptible to malaria infection due to immunological and physiological changes, resulting in adverse maternal and fetal outcomes including maternal anemia, intrauterine growth restriction, preterm birth, low birth weight, and increased neonatal mortality. Consequently, prompt and effective antimalarial treatment is not only a therapeutic necessity but also a public health imperative. Historically, chloroquine was the mainstay of malaria treatment owing to its safety, affordability, and ease of administration [4]. However, the widespread emergence of chloroquine-resistant *P. falciparum* has rendered it largely ineffective in many regions [5, 6]. This resistance prompted a paradigm shift towards artemisinin-based combination therapies (ACTs), which are currently endorsed by the World Health Organization as the first-line treatment for uncomplicated malaria. ACTs combine a fast-acting artemisinin derivative with a longer-acting partner drug, enhancing therapeutic efficacy while mitigating resistance development. Pregnant women, however, represent a unique subpopulation in antimalarial treatment strategies due to concerns over drug safety, pharmacokinetics, and potential teratogenic effects [7]. While chloroquine has a long-established safety profile in pregnancy, its declining efficacy has necessitated the re-evaluation of ACTs for this group. There remains a clinical and ethical imperative to assess the comparative effectiveness of these two treatment classes in terms of parasite clearance, maternal and fetal safety, and prevention of recrudescence. This review synthesizes current evidence on the comparative effectiveness of ACTs versus chloroquine in achieving malaria

clearance among pregnant women. Drawing on randomized controlled trials, cohort studies, and pharmacovigilance data, the review examines treatment efficacy, safety profiles, and contextual considerations, aiming to inform policy decisions and clinical guidelines for malaria management in pregnancy.

Pharmacological Overview of ACTs and Chloroquine

Artemisinin-based combination therapies exert their antimalarial effect through rapid reduction of parasitemia during the asexual erythrocytic stages of *P. falciparum* [8]. Artemisinin derivatives such as artesunate and artemether act by generating reactive oxygen species within the parasite, leading to cellular damage and death. The combination with longer-acting agents such as lumefantrine, amodiaquine, or piperaquine ensures sustained antimalarial activity, targeting residual parasites and preventing recrudescence. Chloroquine, a 4-aminoquinoline compound, functions by interfering with heme detoxification in the parasite's food vacuole, leading to toxic accumulation and parasite death [9]. It has historically been highly effective against *P. vivax* and *P. falciparum*; however, mutations in the *pfcrt* gene have led to widespread resistance, particularly in sub-Saharan Africa and parts of Asia. In pregnancy, pharmacokinetics is altered due to increased plasma volume, altered hepatic metabolism, and changes in drug binding proteins. These changes can affect both efficacy and safety. Importantly, while artemisinin derivatives are not recommended in the first trimester due to insufficient teratogenicity data, several studies have reported favorable outcomes with second- and third-trimester use. Chloroquine, though safe across all trimesters, is increasingly ineffective in many endemic areas.

Efficacy of Parasite Clearance

One of the primary outcomes in malaria treatment efficacy is the speed and completeness of parasite clearance [10]. Numerous trials have consistently demonstrated superior parasite clearance times with ACTs compared to chloroquine. In several studies, ACTs achieved parasite clearance within 48–72 hours, a marked improvement over chloroquine, particularly in regions with high resistance levels.

For example, comparative trials conducted in East Africa reported clearance rates exceeding 95% on day 28 with ACTs such as artemether-lumefantrine, versus under 60% with chloroquine [11]. The presence of chloroquine-resistant strains in these populations significantly undermines its utility, even when parasitemia appears initially responsive.

Additionally, the risk of recrudescence defined as the recurrence of parasitemia due to treatment failure is substantially lower with ACTs. This finding is particularly critical in pregnancy, where repeated episodes of parasitemia can contribute to placental malaria, fetal growth restriction, and stillbirth. ACTs, through their dual mechanism, effectively reduce the reservoir of infection, offering a more reliable therapeutic outcome.

Safety and Tolerability in Pregnancy

Drug safety during pregnancy is paramount due to the potential for teratogenicity and fetal toxicity [12]. Chloroquine, having been used extensively for over five decades, has a well-characterized safety profile and is considered safe across all trimesters. However, its ineffectiveness in many endemic regions significantly compromises its utility despite this advantage.

ACTs, particularly those involving artemether-lumefantrine, have undergone increasing scrutiny with respect to their safety in pregnancy [13]. Although concerns remain regarding their use in the first trimester due to limited human data, large-scale observational studies and surveillance programs have provided reassuring findings in later pregnancy stages. Data from the Malaria in Pregnancy Consortium and similar initiatives suggest no significant increase in adverse pregnancy outcomes including miscarriage, stillbirth, or congenital anomalies with ACT exposure in the second and third trimesters.

Tolerability is also a consideration, particularly regarding gastrointestinal side effects, palpitations, or neurotoxicity [14]. ACTs are generally well tolerated, though lumefantrine-containing combinations may cause transient QT prolongation, necessitating caution in patients with underlying cardiac conditions. Chloroquine, while typically well tolerated, has been associated with pruritus and, at higher doses or prolonged use, retinopathy.

Overall, the safety profiles of ACTs in late pregnancy are increasingly favorable, justifying their use in the context of chloroquine resistance and life-threatening parasitemia.

Impact on Maternal and Neonatal Outcomes

Beyond parasitological cure, antimalarial therapy in pregnancy must be evaluated based on maternal and neonatal outcomes. Malaria in pregnancy is associated with anemia, preeclampsia, low birth weight, and increased perinatal mortality [15]. The ability of an antimalarial regimen to mitigate these risks is therefore a critical indicator of therapeutic success.

Evidence from comparative studies suggests that ACT-treated women experience fewer adverse outcomes than those treated with chloroquine in regions with high resistance prevalence [16]. For instance, maternal hemoglobin levels at delivery are significantly higher among ACT recipients, attributable to more complete parasite clearance and reduced anemia incidence. Neonatal outcomes, including birth weight and Apgar scores, also favor ACTs in resistant settings.

However, in regions where chloroquine resistance is low or absent such as parts of Central America or Haiti chloroquine may still offer comparable outcomes, given its safety profile and low cost. Thus, local epidemiological patterns should inform drug selection.

Resistance and Recrudescence Concerns

One of the central rationales for ACT use is its ability to delay resistance development [17]. The combination of fast-acting and long-acting agents decreases the probability of parasite survival and selection pressure. Nonetheless, emerging resistance to artemisinin and its partner drugs particularly in Southeast Asia raises important concerns.

Chloroquine resistance, in contrast, has remained relatively stable over time, though resurgence in sensitivity has been reported in isolated cases where drug pressure was removed [18]. This phenomenon has reignited interest in chloroquine re-introduction under stringent monitoring in select areas.

In pregnant populations, the implications of resistance are magnified due to potential treatment failure and its consequences. Monitoring molecular markers such as *pfcrt* for chloroquine and *kelch13* for artemisinin resistance should be integrated into public health surveillance, informing local treatment guidelines.

Contextual and Health System Considerations

The selection of antimalarial therapy in pregnancy must also account for broader health system variables, including drug availability, cost, supply chain reliability, and provider training [19]. ACTs are often more expensive and require multiple doses, which may challenge adherence, particularly in low-resource settings. Chloroquine, conversely, is inexpensive, widely available, and familiar to health workers.

However, reliance on an ineffective drug due to cost concerns can be more detrimental in the long term, contributing to ongoing transmission, maternal morbidity, and neonatal complications. Cost-effectiveness analyses suggest that, despite their higher upfront cost, ACTs result in fewer hospital admissions, improved birth outcomes, and lower overall healthcare expenditures in high-burden regions.

Moreover, patient education and health worker training are pivotal in ensuring appropriate drug use and adherence, especially in vulnerable populations such as pregnant women. Community-based strategies, mobile health interventions, and targeted antenatal outreach can enhance access to effective antimalarial treatment.

Comparative Effectiveness in Trimester-Specific Use

An important dimension of comparative analysis concerns gestational age. While ACTs are contraindicated in the first trimester in many guidelines, newer studies are beginning to challenge this restriction [20]. Preliminary data suggest that when used judiciously and under close monitoring, ACTs may not pose a greater risk than quinine, the alternative for early pregnancy.

Chloroquine, with its established safety, remains the drug of choice were effective. In the absence of resistance, it can be safely used across all trimesters. Nonetheless, the vast heterogeneity in resistance patterns underscores the need for regionally tailored protocols.

Thus, trimester-specific guidelines should integrate current resistance data, safety profiles, and clinical urgency. In life-threatening cases, the benefits of effective treatment may outweigh theoretical risks, justifying ACT use under expert supervision even in early pregnancy.

CONCLUSION

Malaria in pregnancy remains a significant driver of maternal and perinatal morbidity and mortality, necessitating safe and efficacious treatment options. Artemisinin-based combination therapies offer clear advantages over chloroquine in terms of rapid parasite clearance, reduced recrudescence, and improved maternal and neonatal outcomes, particularly in regions with high chloroquine resistance. Although concerns regarding the use of ACTs in the first trimester persist, growing evidence supports their safety in the second and third trimesters, making them the preferred option in most clinical scenarios where resistance compromises chloroquine efficacy. Chloroquine continues to have a role in malaria management during pregnancy in regions with documented sensitivity, offering a low-cost, safe, and familiar alternative. However, reliance on chloroquine in resistant settings is not only ineffective but also detrimental to maternal and fetal health. Treatment decisions must therefore be guided by local resistance patterns, gestational age, and available resources. The integration of ACTs into antenatal malaria treatment protocols represents a significant advance in maternal health, but requires sustained investment in pharmacovigilance, health worker training, and supply chain management. Moving forward, continued research and region-specific policy development are essential to optimize malaria management in pregnancy and reduce the global burden of malaria-related complications.

REFERENCES

1. Milner, D.A., Vareta, J., Valim, C., Montgomery, J., Daniels, R.F., Volkman, S.K., Neafsey, D.E., Park, D.J., Schaffner, S.F., Mahesh, N.C., Barnes, K.G., Rosen, D.M., Lukens, A.K., Van Tyne, D., Wiegand, R.C., Sabeti, P.C., Seydel, K.B., Glover, S.J., Kamiza, S., Molyneux, M.E., Taylor, T.E., Wirth, D.F.: Human cerebral malaria and Plasmodium falciparum genotypes in Malawi. Malar J. 11, 35 (2012). https://doi.org/10.1186/1475-2875-11-35

2. Erisa, K., Okechukwu, U., Alum, E.U.: Exploration of Medicinal Plants Used in the Management of Malaria in Uganda. NEWPORT INTERNATIONAL JOURNAL OF RESEARCH IN MEDICAL SCIENCES 4(1):101-108. https://nijournals.org/wp-content/uploads/2023/10/NIJRMS-41101-108-2023.docx.pdf
3. Obeagu, E.I.O., Alum, E.U., Ugwu, O.P.C.: Hepcidin: The Gatekeeper of Iron in Malaria Resistance. NEWPORT INTERNATIONAL JOURNAL OF RESEARCH IN MEDICAL SCIENCES. 4, 1–8 (2023). https://doi.org/10.59298/NIJRMS/2023/10.1.1400
4. Alum, E. U., Tufail, T., Agu, P. C., Akinloye, D. I., & Obaroh, I. O. (2024). Malaria pervasiveness in Sub-Saharan Africa: Overcoming the scuffle. *Medicine*, *103*(49), e40241. doi: 10.1097/MD.0000000000040241.
5. Ige, A.A., Adedokun, T.T., Otutu, O., Olorunfemi, A.B., Ayoola, A.O., Ojurongbe, O.: The Role of the Plasmodium falciparum Chloroquine Resistance Transporter Gene in Malaria Drug Resistance and its implication on malaria control in Africa. (2024). https://doi.org/10.36108/pajols/4202/80.0270
6. Ocan, M., Akena, D., Nsobya, S., Kamya, M.R., Senono, R., Kinengyere, A.A., Obuku, E.A.: Persistence of chloroquine resistance alleles in malaria endemic countries: A systematic review of burden and risk factors. Malar J. 18, 1–15 (2019). https://doi.org/10.1186/S12936-019-2716-Z/TABLES/3
7. Moore, B.R., Davis, T.M.: Updated pharmacokinetic considerations for the use of antimalarial drugs in pregnant women. Expert Opin Drug Metab Toxicol. 16, 741–758 (2020). https://doi.org/10.1080/17425255.2020.1802425
8. Ogbonnia Egwu, C., Aloke, C., Chukwu, J., Agwu, A., Alum, E.U, Tsamesidis, I., M Aja, P., E Offor, C., Ajuka Obasi, N.: A world free of malaria: It is time for Africa to actively champion and take leadership of elimination and eradication strategies. Afr Health Sci. 22, 627–640 (2022). https://doi.org/10.4314/ahs.v22i4.68
9. De Villiers, K.A., Egan, T.J.: Heme Detoxification in the Malaria Parasite: A Target for Antimalarial Drug Development. Acc Chem Res. 54, 2649–2659 (2021). https://doi.org/10.1021/ACS.ACCOUNTS.1C00154/ASSET/IMAGES/MEDIUM/AR1C00154_0005.GIF
10. Khoury, D.S., Zaloumis, S.G., Grigg, M.J., Haque, A., Davenport, M.P., Cromer, D., Rebelo, M., Cao, P., McCaw, J.M., Simpson, J.A., Flegg, J.A., Wilson, D.W., Anstey, N.M., McCarthy, J.S.: Malaria Parasite Clearance: What Are We Really Measuring? Trends Parasitol. 36, 413–426 (2020). https://doi.org/10.1016/J.PT.2020.02.005/ATTACHMENT/F5146A7A-64A4-428F-8982-8AC5962BE2C3/MMC1.DOCX
11. Assefa, D.G., Zeleke, E.D., Bekele, D., Tesfahunei, H.A., Getachew, E., Joseph, M., Manyazewal, T.: Efficacy and safety of dihydroartemisinin–piperaquine versus artemether–lumefantrine for treatment of uncomplicated Plasmodium falciparum malaria in Ugandan children: a systematic review and meta-analysis of randomized control trials. Malar J. 20, 1–25 (2021). https://doi.org/10.1186/S12936-021-03711-4/FIGURES/13
12. Ponticelli, C., Moroni, G.: Fetal Toxicity of Immunosuppressive Drugs in Pregnancy. Journal of Clinical Medicine 2018, Vol. 7, Page 552. 7, 552 (2018). https://doi.org/10.3390/JCM7120552
13. Manyando, C., Kayentao, K., Dalessandro, U., Okafor, H.U., Juma, E., Hamed, K.: A systematic review of the safety and efficacy of artemether-lumefantrine against uncomplicated Plasmodium falciparum malaria during pregnancy. Malar J. 11, 1–13 (2012). https://doi.org/10.1186/1475-2875-11-141/TABLES/4
14. Brodie, M.J.: Tolerability and Safety of Commonly Used Antiepileptic Drugs in Adolescents and Adults: A Clinician's Overview. CNS Drugs 2017 31:2. 31, 135–147 (2017). https://doi.org/10.1007/S40263-016-0406-8
15. Alum, E. U. Phytochemicals in Malaria Treatment: Mechanisms of Action and Clinical Efficacy. KIU J. Health Sci., 4(2):71-84. (2024). https://doi.org/10.59568/KJHS-2024-4-2-06.
16. Beshir, K.B., Diallo, N., Somé, F.A., Sombie, S., Zongo, I., Fofana, B., Traore, A., Dama, S., Bamadio, A., Traore, O.B., Coulibaly, S.A., Maurice, O.S., Diarra, A., Kaboré, J.M., Kodio, A., Togo, A.H., Dara, N., Coulibaly, M., Dao, F., Nikiema, F., Compaore, Y.D., Kabore, N.T., Barry, N., Soulama, I., Sagara, I., Sirima, S.B., Ouédraogo, J.B., Djimde, A., Sutherland, C.J.: Persistent submicroscopic plasmodium falciparum parasitemia 72 hours after treatment with artemether-lumefantrine predicts 42-day treatment failure in Mali and Burkina Faso. Antimicrob Agents Chemother. 65, (2021). https://doi.org/10.1128/AAC.00873-21/ASSET/C31B4DDE-4950-4C76-8223-FA63B2A42C94/ASSETS/IMAGES/LARGE/AAC.00873-21-F0002.JPG
17. Hanboonkunupakarn, B., Tarning, J., Pukrittayakamee, S., Chotivanich, K.: Artemisinin resistance and malaria elimination: Where are we now? Front Pharmacol. 13, 876282 (2022). https://doi.org/10.3389/FPHAR.2022.876282/BIBTEX
18. Balikagala, B., Sakurai-Yatsushiro, M., Tachibana, S.I., Ikeda, M., Yamauchi, M., Katuro, O.T., Ntege, E.H., Sekihara, M., Fukuda, N., Takahashi, N., Yatsushiro, S., Mori, T., Hirai, M., Opio, W., Obwoya, P.S., Anywar,

D.A., Auma, M.A., Palacpac, N.M.Q., Tsuboi, T., Odongo-Aginya, E.I., Kimura, E., Ogwang, M., Horii, T., Mita, T.: Recovery and stable persistence of chloroquine sensitivity in Plasmodium falciparum parasites after its discontinued use in Northern Uganda. Malar J. 19, 1–12 (2020). https://doi.org/10.1186/S12936-020-03157-0/TABLES/3

19. Olaleye, A.O., Walker, O.: Impact of Health Systems on the Implementation of Intermittent Preventive Treatment for Malaria in Pregnancy in Sub-Saharan Africa: A Narrative Synthesis. Tropical Medicine and Infectious Disease 2020, Vol. 5, Page 134. 5, 134 (2020). https://doi.org/10.3390/TROPICALMED5030134

20. Saito, M., McGready, R., Tinto, H., Rouamba, T., Mosha, D., Rulisa, S., Kariuki, S., Desai, M., Manyando, C., Njunju, E.M., Sevene, E., Vala, A., Augusto, O., Clerk, C., Were, E., Mrema, S., Kisinza, W., Byamugisha, J., Kagawa, M., Singlovic, J., Yore, M., van Eijk, A.M., Mehta, U., Stergachis, A., Hill, J., Stepniewska, K., Gomes, M., Guérin, P.J., Nosten, F., ter Kuile, F.O., Dellicour, S.: Pregnancy outcomes after first-trimester treatment with artemisinin derivatives versus non-artemisinin antimalarials: a systematic review and individual patient data meta-analysis. The Lancet. 401, 118–130 (2023). https://doi.org/10.1016/S0140-6736(22)01881-5/ATTACHMENT/D5EDDD40-E603-4AFA-9AAD-DBBF1F223BBB/MMC1.PDF

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