Malaria Prevention during Pregnancy—Is There a Next Step Forward?

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The malaria parasite lives most of its life and does the majority of its replication in red blood cells. The biologically and immunologically unique utero-placental blood space (where the mother’s body must recognize the fetus as not-self and then accept and nurture this foreign body) serves as a near-perfect protected resting and reproducing place for malaria-infected red blood cells—a “holiday spa for parasites.” For a young woman who has grown up with endemic malaria, this protected parasite replication can overcome her acquired systemic malaria immunity and still cause her and her fetus harm in the form of maternal illness, anemia, and premature and low birth weight delivery. For never-exposed young women, the unchecked parasite replication can be catastrophic, leading to severe maternal illness and possible fetal death. Thus, there is no safety from malaria during pregnancy, across the spectrum from very high to very low transmission settings.

This burden of malaria during pregnancy was first described in the scientific literature in 1935 [1] and further elucidated through studies in the 1950s to 1980s [2]; the specific additional burden in HIV-infected women was described in the 1990s as the HIV epidemic spread widely [3,4]. Interventions initially focused on personal protection and, specifically, antimalarial drug prophylaxis [5]. By 1986, the observed high rates of infection at first antenatal care clinic visit led to a recommendation of an initial antimalarial treatment dose to clear those infections, followed by regular prophylaxis [6]; and most of the emphasis was on the use of chloroquine (CQ) as a safe drug, albeit in the midst of evolving parasite resistance to CQ and growing recognition that adherence to weekly CQ prophylaxis was poor and often less than 20% [7,8]. A number of studies in the subsequent years elucidated the value of intermittent preventative treatment in pregnancy (IPTp) using an effective curative dose that also provided prophylaxis and could be given as directly observed therapy (DOT) at an antenatal care clinic. The current WHO recommendation includes IPTp along with good preventive strategies (e.g., consistent use of insecticide-treated mosquito nets) and prompt clinical management of malaria illness using diagnosis and antimalarial treatment [9]. Sulfadoxine-pyrimethamine (SP) became an obvious IPTp alternative after CQ as it was curative, had good prophylaxis duration and was a well-tolerated single-dose treatment that could easily be given as DOT [10]. Unfortunately, antimicrobial drug efficacy never lasts. As with CQ, evolving SP resistance was just a matter of time and in the last decade has emerged across much of Africa [11]. Investigators began testing the next options, and as Menéndez and colleagues describe in this issue of PLOS Medicine [12,13], it is not easy to find the next safe and well-tolerated, single-dose drug that elicits prompt parasite clearance.

Linked Research Articles

This Perspective discusses the following new studies published in PLOS Medicine:

González R, Mombo-Ngoma G, Ouédraogo S, Kakolwa MA, Abdulla S, et al. (2014) Intermittent Preventive Treatment of Malaria in Pregnancy with Mefloquine in HIV-Negative Women: A Multicentre Randomized Controlled Trial. PLoS Med 11(9): e1001733. doi:10.1371/journal.pmed.1001733

Clara Menéndez and colleagues conducted an open-label randomized controlled trial in HIV negative pregnant women in Benin, Gabon, Mozambique, and Tanzania to evaluate the safety and efficacy of mefloquine compared to sulfadoxine-pyrimethamine for intermittent preventative therapy for malaria.

González R, Desai M, Macete E, Ouma P, Kakolwa MA, et al. (2014) Intermittent Preventive Treatment of Malaria in Pregnancy with Mefloquine in HIV-Infected Women Receiving Cotrimoxazole Prophylaxis: A Multicenter Randomized Placebo-Controlled Trial. PLoS Med 11(9): e1001735. doi:10.1371/journal.pmed.1001735

Clara Menéndez and colleagues conducted a randomized controlled trial among HIV positive pregnant women in Kenya, Mozambique, and Tanzania to investigate the safety and efficacy of mefloquine as intermittent preventative therapy for malaria in women receiving cotrimoxazole prophylaxis and long-lasting insecticide treated nets.
and prophylaxis benefit for suitable duration and that can be given as DOT. Their effort to explore whether a low treatment dose (15 mg/kg) of mefloquine (MQ) would be suitable as an alternative to SP for IPTp in HIV-negative women or as IPTp in combination with daily cotrimoxazol in HIV-positive women, showed that reduced rates of malaria infection and maternal illness could be obtained by this efficacious drug, but no obvious added benefit for fetal maturation and growth could be shown for either HIV-negative or HIV-positive women. And, MQ was simply not well tolerated: nausea and dizziness were frequent and potentially debilitating. Previous concerns about the possible association between MQ and fetal loss [14] seem to have been allayed by this study, but the limited added benefit and the poor tolerance still keeps it from being recommended. This report on MQ and its failure to become a viable alternative to SP for IPTp is not alone. Late last year, Pfizer stopped supporting trials of CQ+azithromycin for IPTp [personal communications: George Jagoe, Medicines for Malaria Venture, July 22, 2014] because early results suggested no additional benefit compared to IPTp with SP. As Menéndez and colleagues note, the current WHO recommendations for IPTp with SP remain unchanged.

Luckily, IPTp with SP still demonstrates substantial value in the presence of documented SP-resistance and growing frequency of mutant markers signifying resistance to SP-resistance and growing frequency. With special reference to the transplacental passage of parasites from the maternal to the foetal circulation. Br J Obstet Gynaecol 42: 816–834.

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