Malaria in pregnancy: a call for a safe, efficient, and patient-centred approach to first-trimester treatment

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World Malaria Day 2018 is themed "Ready to beat malaria", but circulated key talking points ignore an important group: pregnant women. Unpublished reports from Médecins Sans Frontières (MSF) programmes, in contexts where up to 50% of women attending antenatal care routinely test positive for malaria, suggest that current WHO recommendations on malaria in pregnancy[1] cause confusion and may risk poor outcomes in this highly vulnerable population.

Malaria during pregnancy can lead to maternal anaemia, miscarriage, stillbirth, and low birthweight, and pregnant women are at a high risk of infection, with the highest burden in the first and second trimesters.[2,3] Quality treatment and prevention is essential to protect both mother and child. Current WHO guidance on treatment of uncomplicated *Plasmodium falciparum* malaria[1] recommends artemisinin-based combination therapies (ACTs) in the second and third trimesters, but quinine in the first, owing to concerns over embryo toxicity with early exposure to artemisinins.

Observational studies show that ACTs are safe in the first trimester (ethical concerns having precluded first-trimester randomised trials). In their meta-analysis of prospective observational studies of first trimester ACTs or quinine, Dellicour and colleagues[4] found no difference in the risk of miscarriage, stillbirth, or major congenital anomalies. In a secondary analysis, quinine in early pregnancy was associated with increased risk of miscarriage compared with pregnancies in which malaria treatment was not required, but there was no such significant association for women treated with ACTs. However, the authors suggest that the increased risk of miscarriage associated with quinine might be confounded by malaria itself being a miscarriage risk and thus reflect inadequately treated malaria due to the long treatment course, poor tolerability, and associated poor patient compliance.[4] In a meta-analysis by Burger and colleagues,[5] the use in pregnancy of ACTs administered once or twice daily for 3 days compared with a 7-day course of 8-hourly quinine was associated with lower prevalence of side-effects, including vomiting (pooled relative risk 0·33, 95% CI 0·15–0·73)—a side-effect that would be particularly distressing in first trimester.

ACTs may be more effective than quinine in pregnancy. They are associated with a longer time to recurrence than quinine in pregnant women[6] and are known to exert a post-treatment protective effect,[7] which may be important in a group where other preventative measures have poor uptake and coverage. For instance, fewer than 39% of women slept under a bednet in 2014,[8] and only 19% of eligible pregnant women received three or more doses of intermittent preventative therapy in 2016.[9]

In a recent unpublished survey of MSF projects with malaria in pregnancy activities (Chiara Morrison, MSF London, personal communication), a third of sites reported using ACTs in first trimester pregnancies, citing side-effects and confusion with protocols for other trimesters as the main reasons for not administering quinine. Worryingly, although intravenous artesunate is the first-line treatment for all pregnant women with severe malaria in all trimesters,[1] 50% of projects surveyed gave intravenous quinine to patients with severe malaria in the first trimester. All projects cited confusion around guidelines and differences with Ministry of Health protocols as the main barriers to use of intravenous artesunate. Our inference from this work is that the recommendation of different drugs in different trimesters for uncomplicated malaria leads to confusion in the management of severe malaria, with potentially severe consequences.

As a result of these issues, the new MSF malaria strategy advocates the use of ACTs for *P falciparum* malaria in all trimesters of pregnancy. We have taken this decision based on current evidence as well as being guided by a patient-centred and access approach: ACTs are at least as effective and more efficient than quinine, and possibly safer given worries around tolerability and compliance with quinine. Compliance begins with the prescriber, and here we promote a shorter and more tolerable treatment course with less frequent dosing to enable compliance by the patient, thereby reducing the risk of adverse outcomes from partially treated malaria. This is especially relevant for chaotic contexts such as displacement, conflict, or outreach to communities with poor access where malaria thrives.[9] Importantly,

using ACTs in all trimesters may also have secondary safety implications if a simpler guideline means that women with severe malaria are not treated with inferior regimens of intravenous quinine. WHO's Malaria Policy Advisory Committee has recommended that guidelines for treatment of malaria in the first trimester of pregnancy be revised.[10] We strongly support this recommendation, and urge WHO to follow our position and thus reduce barriers to access to the best quality care for pregnant women.

V Bhargavi Rao, Tomas O Jensen, B Carolina Jimenez, Jo Robays, Estrella Lasry, Esther Sterk, Martin de Smet (The MSF Malaria Working Group)
Médecins Sans Frontières, London, UK (VBR); Médecins Sans Frontières, Paris, France (TOJ); Médecins Sans Frontières, Barcelona, Spain (BCJ, EL); Médecins Sans Frontières, Brussels, Belgium (JR, MdS); and Médecins Sans Frontières, Geneva, Switzerland (ES)
bhargavi.rao@london.msf.org

We declare no competing interests.

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