Research team finds no adverse risk to use of common antimalarials in first trimester of pregnancy

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LSTM, University of Washington and international researchers publish the most comprehensive international analysis on artemisinin combination antimalarials safety in pregnancy

Malaria is more common and severe in pregnant women, increasing their risk of miscarriage and other adverse outcomes. The adverse consequences of malaria in pregnancy require prompt, safe, and effective treatment. However, limited data on the safety of the most efficacious and widely used antimalarial medications, artemisinin combination therapies (ACTs), has prevented ACTs from being recommended in the first trimester except in life-saving circumstances. The World Health Organization currently recommends the use of ACTs in pregnant women in the 2nd or 3rd trimester.

An international collaboration led by first authors Stephanie Dellicour of the Liverpool School of Tropical Medicine, UK, and Esperança Sevene of the Manhiça Health Research Centre/Eduardo Mondlane University, Maputo, Mozambique, and senior author Andy Stergachis of University of Washington School of Pharmacy and School of Public Health released the largest meta-analysis of all observational studies-to-date showing there was no difference in the risk of miscarriage, still births or major birth defects associated with the use of artemisinins anytime during the first trimester, compared with quinine. The study, "First-trimester artemisinin derivatives and quinine treatments and the risk of

adverse pregnancy outcomes in Africa and Asia: A meta-analysis of observational studies," was published in *PLoS Medicine* and coordinated through the Malaria in Pregnancy Consortium, established in 2007 at the Liverpool School of Tropical Medicine to improve the control and prevention of malaria in pregnancy.

"This study is clearly significant and reflects many years of work in Thailand and Africa by a large group of scientists," said LSTM's Professor Feiko ter Kuile, head of the Malaria in Pregnancy consortium. "We have been able to show that artemisinins, which we know to improve outcomes in malaria, are as safe to use in the first trimester as quinine, which is currently recommended in the first trimester, but needs to be taken 3 times per day for 7 days. Quinine is associated with transient side effects such a ringing in the ears and dizziness, leading women not to complete their treatment course and risking inadequately treating their malaria. The artemisinin-based combinations are more efficacious, much better tolerated and can be taken over three days."

The team analyzed data from five studies involving 30,618 pregnancies: four studies from Zambia, Tanzania, Rwanda, Kenya, Mozambique, Burkina Faso, and one large study from the Thailand based Shoklo Malaria Research Unit. They examined the records of women who had taken artemisinins for malaria, including during the first trimester of pregnancy. In malaria endemic countries, many early pregnancies are advertently or inadvertently exposed to artemisinins because women are not aware they are pregnant or do not report an early pregnancy.

The team summarized all available safety data on the effect of artemisinin exposure in the first trimester and compared the risk of miscarriage, stillbirth, and major congenital anomaly for pregnancies treated with artemisinin, quinine, or no antimalarials in the first trimester.

Through their meta-analysis, they determined the risk of miscarriages, stillbirths, and major anomalies associated with first-trimester artemisinin treatment versus quinine. The results were then combined with summary effect estimates from the Shoklo Malaria Research Unit on the Thailand-Myanmar border.

They found no increase in the risk of miscarriage, stillbirth, or major birth defects associated with the use of artemisinins anytime during the first trimester compared with the use of quinine during the same gestational period. These findings suggest that the artemisinin class of antimalarials should be considered for treatment of malaria in the first trimester of pregnancy. The limited data on the risk of birth defects require further observational studies.

Limited safety data on the use of artemisinins in human pregnancies have historically prevented health authorities from recommending these therapies for malaria treatment in the first trimester, except in life-saving circumstances. It is possible that this study may result in a major change to recommended guidelines for the administration of artemisinins in the first trimester of pregnancy.

"Our results show that artemisinins can now be formally considered for first trimester treatment," said Andy Stergachis, Professor of Pharmacy and Global Health, University of Washington. While there is more work to be done in terms of monitoring birth defects, the available evidence suggests that the benefits of using this class of antimalarial are likely to outweigh any adverse outcomes and could help save the lives and maintain the pregnancies of women when they are most vulnerable to malaria."

More information: Stephanie Dellicour et al. First-trimester artemisinin derivatives and quinine treatments and the risk of adverse pregnancy outcomes in Africa and Asia: A meta-analysis of

observational studies, *PLOS Medicine* (2017). DOI: 10.1371/journal.pmed.1002290