Research News

April 29, 2020
The Institute of Medical Science
The University of Tokyo
http://www.ims.u-tokyo.ac.jp/imsut/en/
The WorldWide Antimalarial Resistance Network
https://www.wwarn.org/

New evidence for optimising malaria treatment in pregnant women

－Findings that ACTs were significantly more effective than quinine －

The research, published in The Lancet Infectious Diseases is the fruit of joint project between investigators from around the world to conduct the largest individual patient data meta-analysis to date under The WorldWide Antimalarial Resistance Network（WWARN）umbrella. The study found that artemether-lumefantrine (AL) (*1) and other artemisinin-based combination therapies (ACTs) (*2) were significantly more effective than quinine, the current recommended treatment. Authors urgently call for further investigation into dose optimisation for pregnant women to ensure the highest possible treatment success. A joint research group consisting of WWARN, The Nuffield Department of Medicine, University of Oxford and The Institute of Medical Science, The University of Tokyo announced on the 29 th (GMT).

An estimated 125 million pregnant women are at risk of malaria every year

Pregnant women are particularly susceptible to malaria, with the infection adversely affecting both mother and fetus. An estimated 60% of pregnant women in the world live in malaria endemic regions, with 125 million pregnant women at risk every year. Despite this, expectant mothers have been hugely understudied in antimalarial clinical trials. Typically, this group was excluded from clinical trials due to concerns over drug safety on the fetus, however the last two decades have seen increasing evidence that commonly used malaria

treatments are in fact safe. Despite this, there are no agreed guidelines to assess antimalarial drug efficacy during pregnancy.

At present, quinine with clindamycin is the recommended drug to treat women during their first trimester of pregnancy. However, clindamycin is not widely available in malaria-endemic areas and quinine monotherapy is commonly used throughout all trimesters.

In this study, WWARN conducted an individual patient data meta-analysis of existing data from 4,968 pregnant women from 19 studies across 10 countries – representing 92% of patients in the available literature. Pooling and standardising the data from many regions and time-periods into a single dataset for analyses increases the statistical power needed to address key knowledge gaps, particularly when the existing data is sparse. Researchers assessed the efficacy and tolerability of quinine-based treatments and ACTs, including AL, the most commonly used ACT.

"Pregnant women no longer have to put up with quinine"

Authors found that the efficacy and tolerability of ACTs was better than that for quinine. AL had the best tolerability, but the lowest efficacy in comparison to other ACTs. Authors suggest the lower efficacy may be because dosing of AL is too low and recommend further investigation into dose optimisation.

The lead author of the study, Dr Makoto Saito, Assistant Professor at The Institute of Medical Science, The University of Tokyo(IMSUT) says: "As the safety of ACTs have been shown previously, the most efficacious drug with fewer side effects should be used to minimise the adverse impact of malaria on mother and fetus. Although the current dosing of ACT for pregnant women may not be optimal, pregnant women no longer have to put up with quinine."

"We found that women in their first pregnancy or with higher malaria parasite burden were at a higher risk of treatment failure and should be carefully monitored"

Regardless of transmission intensity, over 95% of women treated with all ACTs except AL were free of recurrence

In high malaria transmission areas, there was recurrence of falciparum malaria in 58.0% of women within 28 days of quinine treatment, while there was 13.8% recurrence after AL

treatment. In low transmission areas, both treatments were more efficacious but 33.6% of women treated with quinine had recurrence within 28 days. Regardless of transmission intensity, over 95% of women treated with all other ACTs were free of recurrence.

Presence of gametocytes(*3), the sexual form of malaria parasites, were more frequent after quinine treatment compared with ACTs, this favours the use ACTs as they will be reducing the overall transmission of malaria parasites. Quinine was associated with lower tolerability due to higher risks of side effects such as abdominal pain, nausea and vomiting. This could be further exacerbated by morning sickness in the first trimester, the time during which quinine is recommended. As pregnant women infected with malaria generally have less symptoms than non-pregnant women, they are less likely to tolerate adverse drug events.

Authors caution that updated variable local patterns of resistant to antimalarial treatments should be considered when applying these findings to specific settings, and also both efficacy and tolerability of ACTs need to be re-assessed if a new dosing regimen is proposed for pregnant women.

Prof Philippe Guérin, Director of WWARN and senior author on the study says: "The findings of this study as well as evidence of safety shown in previous research provides compelling evidence that quinine provides lower efficacy and tolerability than ACTs. Further research into drug dosing to ensure optimum treatment effectiveness for both mother and fetus is paramount."

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Research Notes

(*1) **Artemether-lumefantrine (AL)**

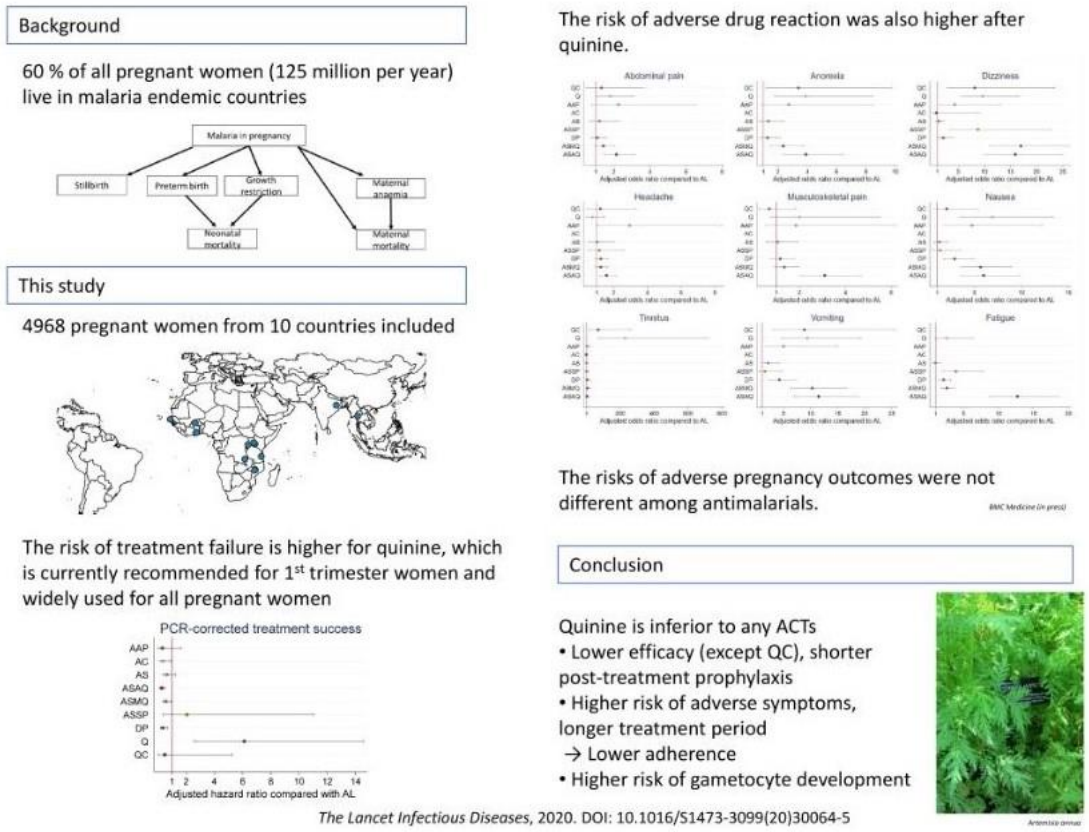
Artemether-lumefantrine consists of an artemisinin derivative (artemether) and another antimalarial with a longer half-life (lumefantrine). AL is the most commonly and widely used ACT in the world.

(*2) **Artemisinin-based combination therapy (ACT)**

Artemisinin-based combination therapy (ACT) is the current standard treatment for uncomplicated falciparum malaria in non-pregnant patients, which has decreased the mortality from malaria dramatically. ACT consists of artemisinin-derivatives and partner drug(s), which has different mechanisms of action and a longer half-life. Artemisinin is derived from an herbal plant (*Artemisia annua*, see picture). The 2015 Nobel Prize was awarded for the discovery of artemisinin. There are several antimalarials that can be combined with artemisinins as a partner drug.

(*3) **Gametocyte**

Gametocytes are the sexual form of malaria parasites, which can be transmitted from infected humans to female mosquitos by mosquito bites. Although gametocytes are not pathogenic by itself, they are thus important for the transmission and control of malaria.



About the research

1) Journal Article

Makoto Saito*, Rashid Mansoor, Kalynn Kennon, Anupkumar R Anvikar, Elizabeth A Ashley, Daniel Chandramohan, Lauren M Cohee,Umberto D'Alessandro, Blaise Genton, Mary Ellen Gilder, Elizabeth Juma, Linda Kalilani-Phiri, Irene Kuepfer, Miriam K Laufer, Khin Maung Lwin,Steven R Meshnick, Dominic Mosha, Victor Mwapasa, Norah Mwebaza, Michael Nambozi, Jean-Louis A Ndiaye, François Nosten, Myaing Nyunt,Bernhards Ogutu, Sunil Parikh, Moo Kho Paw, Aung Pyae Phyo, Mupawjay Pimanpanarak, Patrice Piola, Marcus J Rijken, Kanlaya Sriprawat,Harry K Tagbor, Joel Tarning, Halidou Tinto, Innocent Valéa, Neena Valecha, Nicholas J White, Jacher Wiladphaingern, Kasia Stepniewska, Rose McGready, Philippe J Guérin*.

Efficacy and tolerability of artemisinin-based and quinine-based treatments for uncomplicated falciparum malaria in pregnancy: a systematic review and individual patient data meta-analysis. *The Lancet Infectious Diseases.* 2020

DOI： 10.1016/S1473-3099(20)30064-5

Article URL： https://doi.org/10.1016/S1473-3099(20)30064-5

2）Publication Journal

The Lancet Infectious Diseases

https://www.thelancet.com/journals/laninf/home

3）Related publication

Saito M, Mansoor R, et al. Pregnancy outcomes and risk of placental malaria after artemisinin-based and quinine-based treatment for uncomplicated falciparum malaria in pregnancy: a WorldWide Antimalarial Resistance Network systematic review and individual patient data meta-analysis. BMC Medicine. 2020. DOI: 10.1186/s12916-020-01592-z

4）References

Dellicour S, Tatem AJ, Guerra CA, Snow RW, ter Kuile FO. Quantifying the number of pregnancies at risk of malaria in 2007: a demographic study. PLoS Med 2010; 7(1): e1000221.

Moore KA, Simpson JA, Paw MK, et al. Safety of artemisinins in first trimester of prospectively followed pregnancies: an observational study. Lancet Infect Dis 2016; 16(5): 576-83.

Dellicour S, Sevene E, McGready R, 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 Med 2017; 14(5): e1002290.

5）Related Links

Explore the Malaria in Pregnancy Library to comprehensively search published and unpublished literature related to malaria in pregnancy.

6）Contact

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■ About The WorldWide Antimalarial Resistance Network(WWARN)

The WorldWide Antimalarial Research Network (WWARN)'s mission is to generate innovative tools and reliable evidence to inform the malaria community on the factors affecting the efficacy of antimalarial medicines. WWARN works with collaborators to optimise the efficacy of antimalarial medicines and treatment regimens, especially for vulnerable groups including pregnant women, infants and malnourished children, and provides evidence to inform the development of new antimalarial drugs.

At the request of health communities working on specific infectious diseases, the WWARN model has now been expanded beyond malaria and in 2016 the Infectious Diseases Data Observatory (IDDO) began developing data platforms for emerging and poverty-related infectious diseases. IDDO is actively working on the response to COVID-19 pandemic.

■ About The Institute of Medical Science, The University of Tokyo（IMSUT)

The Institute of Medical Science, The University of Tokyo (IMSUT) evolved from its origin, the Institute for Infectious Disease (founded in 1892). The mission of IMSUT is to advance basic knowledge underlying infectious diseases, cancer and other intractable diseases and ultimately to control them. IMSUT consists of about 165 faculty members, 224 graduate students coming from various schools such as medicine, science, agriculture, pharmaceutical science, and engineering to develop more effective interdisciplinary research in basic life science and genomic medicine.