Maternal malaria during pregnancy causes cognitive defects in the offspring

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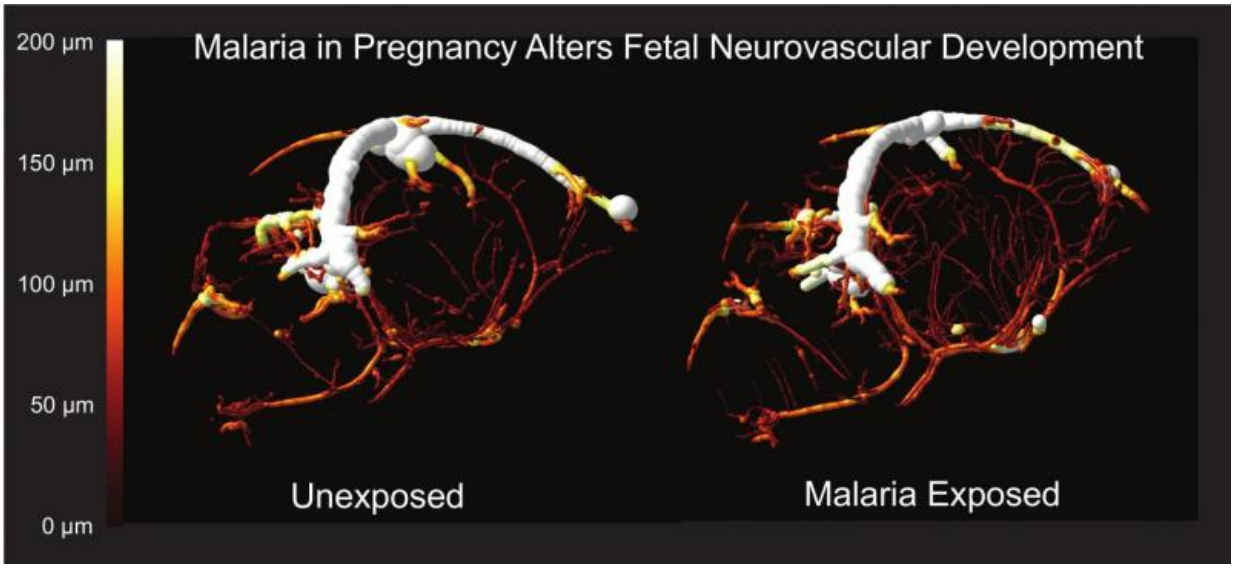

Maternal malaria infection alters the formation of blood vessels in the brains of exposed offspring. The exposed fetus has more small blood vessels in its brain by micro-CT scanning than the control fetus. Credit: CC-BY: McDonald et al.

Over half of all pregnant women world-wide are at risk for malaria, but little is known about possible consequences for the neurodevelopment of children exposed to malaria in pregnancy. A study published on September 24th in *PLOS Pathogens* reports a causal link between pre-natal exposure to malaria and subsequent neurocognitive impairment in offspring in a mouse model of experimental malaria in pregnancy. The

research also identifies some of the molecular mechanisms involved.

Kevin Kain, from the University of Toronto, Canada, and colleagues are interested in health consequences for children exposed to malaria in pregnancy. In this study, they specifically examined neurocognitive function in mice of normal birth weight that had been exposed to—but not themselves infected with—malaria in the uterus (both low birth weight and fetal malaria might also affect neurodevelopment, and were therefore eliminated as possible complicating factors).

The researchers found that young mice that had been exposed to malaria in pregnancy have impaired learning and memory and show depressive-like behavior that persists to adulthood. These neurocognitive impairments are associated with decreased tissue levels of major neurotransmitters (serotonin, dopamine, and norepinephrine) in specific regions of the brain. Pushing the technology by imaging blood vessels in the uterus, the researchers also saw changes in neurovascular development in the brain of malaria-exposed mouse fetuses (see image).

Because a specific immune system factor called C5a had previously been linked to both neurodevelopment and adverse birth outcomes after malaria-exposure in pregnancy, the researchers next tested whether C5a signaling played a role in the link between malaria during pregnancy and neurocognitive impairment they discovered. They found that genetic and functional disruption of maternal C5a signaling restored neurotransmitter levels and completely rescued the neurocognitive defects in the offspring. In other words, mothers with defective C5a signaling that had malaria in pregnancy gave birth to malaria-exposed pups without detectable neurocognitive abnormalities.

These results, the researchers say, "highlight a novel mechanism by which malaria in pregnancy may alter the neurocognitive development of millions of children prior to birth". They mention that "a prospective

study is underway to confirm these findings in African children exposed to malaria in utero". Stressing that "it is essential to identify preventable risk factors that can be modified to decrease the risk of developmental delay in children", they say, "this study suggests that malaria in pregnancy is one such factor that can be targeted [and FDA-approved anti-C5a strategies exist] in order to improve cognitive development and school performance in malaria-endemic regions".

More information: McDonald CR, Cahill LS, Ho KT, Yang J, Kim H, Silver KL, et al. (2015) Experimental Malaria in Pregnancy Induces Neurocognitive Injury in Uninfected Offspring via a C5a-C5a Receptor Dependent Pathway. *PLoS Pathog* 11(9): e1005140. DOI: 10.1371/journal.ppat.1005140

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