Single-dose antibiotic can prevent maternal sepsis and death

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A single oral dose of the antibiotic azithromycin can reduce the risk of postpartum sepsis and death among women who deliver vaginally by one-third, according to a large multi-country clinical trial, called A-PLUS.

Only 1.6% of women in the study who received azithromycin during labor developed sepsis or died within six weeks after delivery, compared to 2.4% of those who received placebo. Azithromycin did not reduce the risk of stillbirth, newborn sepsis or newborn death.

Results from the study, which enrolled more than 29,000 women in seven low- and middle-income countries, were published today in the *New England Journal of Medicine* and presented at the Society for Maternal-Fetal Medicine's 43rd Annual Pregnancy Meeting, San Francisco.

"These findings have the potential to change clinical practice by providing a safe, effective and low-cost approach to reduce the global burden of maternal sepsis and death," said Diana W. Bianchi, M.D., director of NIH's Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), the primary funder of the trial. "We urgently need effective strategies to prevent pregnancy-related infections, which account for roughly 10% of maternal deaths worldwide."

NICHD's Global Network for Women's and Children's Health Research conducted the study.

Sepsis—a life-threatening complication of bacterial and other infections—is a leading cause of maternal and newborn deaths worldwide, especially in low- and middle-income countries. Azithromycin, an inexpensive antibiotic effective against a broad range of bacteria, is known to reduce maternal infection when given intravenously during cesarean delivery. Two small studies have suggested that giving the oral version of the drug to women who plan to deliver vaginally may reduce maternal or neonatal infection and death.

Launched in 2020, A-PLUS enrolled women at NICHD Global Network

sites in Bangladesh, the Democratic Republic of the Congo, Guatemala, India, Kenya, Pakistan and Zambia. Between September 2020 and August 2022, 29,278 participants planning to deliver vaginally were randomly assigned to receive either a two-gram dose of oral azithromycin or a placebo during labor.

Within the first six weeks after delivery, 227 of 14,526 participants (1.6%) who received azithromycin developed sepsis or died, compared to 344 of 14,637 (2.4%) in the placebo group. Deaths were rare in both groups. Sepsis occurred in 219 participants in the azithromycin group (1.5%) and 339 in the placebo group (2.3%). Additionally, women who received azithromycin were less likely to develop endometritis (infection of the lining of the womb) and other infections. They also had fewer hospital readmissions and unscheduled healthcare visits, compared to the placebo group.

"Leveraging the infrastructure and expertise of the NICHD Global Network across three continents allowed us to rapidly gather these important data. We hope that our findings will be applied to help improve maternal care in low- and middle-income countries around the globe," said Alan T.N. Tita, M.D., Ph.D., associate dean of Global and Women's Health of the University of Alabama at Birmingham (UAB) Marnix E. Heersink School of Medicine.

The trial was co-led by Dr. Tita and Waldemar A. Carlo, M.D., also of UAB. Eight U.S. academic institutions and RTI International, Research Triangle Park, North Carolina, which serves as the data coordinating center for the NICHD Global Network, collaborated with eight international partners on A-PLUS.

Stillbirth, newborn sepsis or death within the first four weeks of life occurred with comparable frequencies in the azithromycin and placebo groups. Overall, these adverse events occurred for 10.5% of births in the

azithromycin group and 10.3% in the placebo group.

A-PLUS was originally designed to enroll up to 34,000 women. However, based on a recommendation from the study's independent data and safety monitoring committee following a planned interim data analysis, the study was stopped early due to the clear maternal benefit of azithromycin.

More information: Alan T.N. Tita et al, Azithromycin to prevent sepsis or death in women planning a vaginal birth, *New England Journal of Medicine* (2023). DOI: 10.1056/NEJMoa2212111

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