# Endothelial – The final frontier to reduce preterm birth and death from sepsis

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## Each year, around 15 million babies are born prematurely, with nearly one million dying soon after due to complications. Maternal mortality remains high, particularly in low-resource settings. This article describes how assessing endothelial integrity and function could help identify at-risk pregnancies to prevent adverse outcomes

Adverse pregnancy and birth outcomes remain among the deadliest and most persistent global health challenges. Each year, approximately 15 million babies are born prematurely, and nearly one million die shortly after birth due to complications of prematurity. [1, 2] Neonatal sepsis, particularly in preterm infants, is a leading cause of death in the first weeks of life. Furthermore, maternal mortality remains unacceptably high, with 260,000 women dying during and following pregnancy and childbirth. Most (92%) of these maternal deaths occurred in low-resource settings and could have been prevented. [3] Together, preterm birth and sepsis account for millions of maternal and neonatal deaths worldwide. Despite advances in obstetric and neonatal care, these conditions continue to pose a major public health burden. [4, 5]

### The role of vascular integrity

The lining of blood vessels (vascular endothelium) is a master regulator of blood vessel integrity and is critical for adapting to pregnancy, including placental development. Endothelial dysfunction can trigger preterm birth and drive organ injury and death in maternal as well as neonatal sepsis. [6-9] The key molecular regulators of vascular integrity in pregnancy and during sepsis are nitric oxide (NO), the Angiopoietin- Tie2 pathway, and vascular growth factors. Pioneering work, including that of Dr Kevin Kain at the University of Toronto, highlights L-arginine (L-Arg), the precursor to NO, as a powerful vascular stabilizer linked to a lower risk for preterm birth. [10-12] And angiopoietin-1 (Ang1) analogues support vascular stability in preclinical studies. [13] Thus, across pregnancy and sepsis, molecular and cellular pathways that support vascular integrity offer a unified approach to strengthen endothelial stability. Emerging data support this universal approach. Oral L-Arg (and/or L-citrulline – which converts to L-Arg in vivo, tastes better, and has less gastrointestinal degradation) is safe in pregnancy, and in neonatal sepsis models, L-Arg and Ang1 each improve survival, but their combination protects nearly all. Ongoing trials testing maternal L-Arg to reduce preterm birth and neonatal sepsis highlight the promise of Ang1/L-Arg therapy as a single vascular-protective intervention for high-risk populations such as pregnant women and newborn babies. [14, 15]

### Early identification of at-risk pregnancies to prevent adverse outcomes

Preventing adverse pregnancy outcomes and death from sepsis requires identifying at-risk cases early enough to intervene. Most current screening tools rely on symptoms that appear late in the course, often when it is too late to change the outcome. [16] Vascular biology offers a

new opportunity. Endothelial integrity and function can be accessed via blood-based biomarkers. [17-22] The endothelium can also be assessed through non-invasive methods. One promising approach is retinal imaging using optical coherence tomography angiography (OCT-A), which captures subtle changes in the blood vessels at the back of the eye. The retina shares embryologic and physiological similarities with systemic vasculature, making it a powerful 'window' into endothelial health. Alterations in retinal vessel caliber or flow patterns can signal systemic vascular dysfunction long before clinical symptoms appear. [23, 24]

At Dalhousie University, we are exploring how endothelial signaling pathways, particularly those involving angiopoietins and nitric oxide, shift during pregnancy and sepsis. These pathways determine how well blood vessels respond to infection and inflammation. Understanding their disruption could identify early warning signs and therapeutic targets to stabilize vascular health in both mothers and infants. Combining such endothelial biomarkers with Artificial Intelligence (AI)-driven analytics could transform early risk prediction from theory into practice. Machine Learning models trained on physiological, retinal, and molecular data can help identify pregnancies at risk of preterm birth or infection long before a crisis strikes. [20, 25, 26]

The ultimate challenge is translating this insight into accessible, equitable care. Even the most advanced diagnostic tools are ineffective if they cannot reach the populations who need them most. Historically, efforts against preterm birth, maternal and neonatal sepsis have focused on clinical management after complications arise. True prevention begins much earlier, at the microscopic interface where blood meets tissue: the endothelium. By studying, monitoring, and strengthening this vascular frontier, we can detect risk before symptoms emerge, personalize interventions, and prevent the cascade of inflammation and infection that leads to preterm birth and death. The endothelium is more than a passive lining; it is a critical gatekeeper of health and disease. Recognizing and protecting it may be the final frontier in safeguarding mothers and newborns and transforming global pregnancy outcomes. [6, 27]

The endothelium serves as the body's key regulator of vascular health. Protecting it offers a practical and relevant strategy to prevent preterm birth and reduce sepsis-related deaths. Integrating early detection, AI-driven risk prediction, and vascular-targeted therapies can transform maternal and neonatal health, enabling equitable, scalable interventions that save lives globally.

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