Lead Author Q&A – Nerea Castillo Marco

Simple blood test detects preeclampsia risk months before symptoms appear, new study shows

1. What motivated your team to explore cfRNA as a tool for preeclampsia screening early in pregnancy?

   Preeclampsia remains one of the leading causes of maternal and perinatal morbidity and mortality worldwide. Early detection is key to enabling timely interventions that can significantly improve outcomes for both mother and child. In our previous research, we identified a crucial early defect in the uterus: decidualisation resistance, a failure in the proper transformation of the endometrial lining that supports embryo implantation and placental development. This insight led us to ask whether such early pathological processes in the uterine environment could be detected non-invasively in maternal blood.

   Cell-free RNA (cfRNA) offered a promising solution —as a liquid biopsy, it reflects molecular signals released from multiple maternal tissues, including the uterus and the placenta. This gave us a unique opportunity to explore early biomarkers of preeclampsia, long before clinical symptoms emerge.

2. How does this method improve on current preeclampsia prediction methods?

   Current screening methods for preeclampsia still fall short, especially in terms of early detection. Tools based solely on maternal risk factors, such as age or medical history, miss more than half of the cases (sensitivity <41%). Biomarker tests that measure placental dysfunction —like sFLT1 and PlGF— are more accurate, but are typically used later in pregnancy, around 23 weeks, and mostly in women already showing signs of the disease. Although these markers can be applied earlier, in the first trimester, they require a complex combination of clinical variables, and their limited performance and lack of standardised protocols have hindered routine use.

   Our cfRNA-based approach introduces a new dimension: a standardised, non-invasive molecular test that captures subtle signals from across maternal tissues— including the uterus and placenta. It enables reliable identification of at-risk pregnancies weeks to months before symptoms emerge, offering the chance to begin personalised monitoring and preventive care much earlier in gestation.

3. Were there any unexpected or surprising findings within your study?

Yes — beyond building accurate predictive models, our study revealed new biological insights into the distinct mechanisms driving early-onset (EOPE) and late-onset (LOPE) preeclampsia. One of the most remarkable findings was that the model's strongest predictive signals were driven by cfRNAs linked to genes involved in decidualisation resistance — a hallmark of uterine dysfunction. This supports our hypothesis that early molecular defects in the uterine environment are a key contributor to EOPE.

This molecular signature enabled the model to identify high-risk pregnancies up to 18 weeks before clinical diagnosis, providing a valuable window for early intervention. The high performance of the test highlights the clinical potential of integrating uterine biology into screening strategies.

In parallel, our transcriptomic analyses showed that EOPE involves widespread molecular changes across organs, including liver, kidney, placenta, brain, and lungs, while LOPE displayed later-onset and more localised patterns, particularly in immune and hepatic pathways. These insights emphasise that EOPE and LOPE are distinct disease entities with different severities, timelines, and underlying biology. Ultimately, advancing early prediction will require a systems-level understanding of maternal-foetal interactions, encompassing uterine, placental, and systemic contributions to disease development.

4. How do the distinct cfRNA signatures of early-onset and late-onset preeclampsia help us better understand their different underlying causes?

cfRNA profiling gave us a unique opportunity to follow the molecular progression of preeclampsia throughout pregnancy. By analysing samples at three key stages —the first, second, and third trimesters— we were able to reconstruct longitudinal molecular trajectories for each patient.

This revealed that EOPE is characterised by early, escalating disruptions in cfRNA profile involving multiple tissues such as the decidua, placenta, liver, and kidneys. These alterations often began weeks before clinical diagnosis. In contrast, LOPE showed a more delayed and restricted molecular profile, primarily involving immune and hepatic signals closer to symptom onset.

By tracking how and when different organ systems become involved, cfRNA allows us to move beyond symptom-based classification and instead define preeclampsia subtypes based on their biological course. This deeper understanding supports the

development of more individualised monitoring and care pathways tailored to each subtype's molecular dynamics.

5. What are they key next steps for validating the test, and what timeline do you foresee for wider clinical use?

To move toward clinical implementation, the next critical step is to validate our cfRNA-based predictive models in larger, more diverse, real-world populations. While our initial results are promising, broader validation is essential to ensure consistent performance across different clinical settings and demographics.

We are currently conducting a prospective clinical study (ClinicalTrials.gov Identifier: NCT06716242) designed to assess the utility and feasibility of cfRNA screening in standard prenatal care. This trial will help define how the test performs under real-world conditions, including its integration into clinical workflows.

With validation and regulatory efforts already underway, we anticipate that cfRNA-based screening could become available in clinical practice within the next year — offering an unprecedented opportunity for early, non-invasive identification of high-risk pregnancies and timely intervention.

6. If this test was widely adopted, how could it potentially change prenatal care and improve outcomes for mothers and babies?

If widely adopted, cfRNA-based testing could reshape prenatal care by enabling earlier and more precise risk stratification for preeclampsia, before symptoms emerge. This would allow clinicians to initiate preventive measures sooner, including low-dose aspirin and structured monitoring of blood pressure, renal function, and foetal growth.

It would also support the use of personalised adjunct strategies, such as nutrition, exercise, and sleep optimisation, based on each patient's biological risk profile. By moving from a reactive to a preventive approach, this test could reduce the incidence of severe complications for both mothers and babies.

Looking ahead, cfRNA analysis may also unlock new therapeutic possibilities. By offering insight into the molecular pathways involved in disease progression, it could inform drug repurposing or support the development of RNA-targeted treatments. In the long term, tracking cfRNA dynamics across pregnancy could help identify the

optimal timing for interventions, further improving outcomes and ushering in a new era of precision obstetric care.