News & views

Human development

A blood test to predict pregnancy complications

Lydia L. Shook & Andrea G. Edlow

Cell-free RNA transcripts in maternal blood can be analysed to monitor the progression of pregnancy and to predict a potentially harmful pregnancy-specific condition called pre-eclampsia. See p.422

The biology of human pregnancy is challenging to study. Invasive diagnostic procedures can be used to obtain DNA from the placenta or fetus for genetic analyses, or to sample RNA for a snapshot of development at that moment in time. For ethical and practical reasons, however, it is not possible to repetitively sample the growing fetus and placenta to monitor development and pregnancy health across gestation. On page 422, Rasmussen *et al.*[1] collect and analyse RNA molecules circulating freely in the bloodstream — known as cell-free RNA (cfRNA) — from more than 1,800 pregnant individuals of various ages, body mass indices and races, from different continents and at different stages of their pregnancies. The analyses provide insight into normal fetal, placental and maternal changes in gene expression across gestation. The authors then use this knowledge of normal cfRNA signatures in pregnancy to predict the development of a potentially dangerous pregnancy complication called pre-eclampsia.

The recognition that cell-free DNA and RNA are released from maternal, fetal and placental tissues and can be detected in maternal plasma (a component of blood) was a landmark advance in pregnancy diagnostics[2]. Next-generation sequencing techniques to detect cell-free fetal DNA (cffDNA) in maternal plasma are now in widespread use to screen pregnancies non-invasively for common fetal chromosomal abnormalities with high sensitivity and specificity[3,4]. Although analysing cffDNA is useful for diagnosing specific fetal genetic conditions, cfRNA is the more dynamic nucleic acid, and offers a snapshot of development in real time by providing insight into which genes are currently being expressed[2].

Pre-eclampsia is characterized by the onset of high blood pressure during pregnancy. It affects about 8% of pregnancies, can cause damage to multiple organ systems, and is a leading cause of severe maternal and neonatal illness and death[5]. Although the signs and symptoms of pre-eclampsia do not typically manifest until the final weeks of pregnancy, the disease originates early, when the placenta is established. Despite centuries-old knowledge of pre-eclampsia, a test to predict the condition early in pregnancy, when an intervention might be able to alter the course of the disease, has remained out of reach.

Much of the research on molecular 'markers' of pregnancy-related disorders has focused on proteins in accessible maternal samples, such as blood or urine[6]. However, Rasmussen and colleagues focused their efforts on analysing cfRNA that arises from maternal, placental and fetal tissues and is released into maternal blood (Fig. 1). The authors assessed the complement of cfRNA molecules found in maternal blood (the transcriptome) from a total of 2,539 plasma samples from 1,840 pregnancies in 8 independent groups — the largest and most diverse transcriptomic pregnancy study performed so far.

The authors built on previous work demonstrating that cfRNA transcripts in maternal plasma could predict gestational age (the developmental age of the fetus)[7]. They used a machine-learning approach to teach an algorithm with a training set of 1,908 cfRNA profiles to predict gestational age. On a separate test set of 474 samples, the algorithm could predict gestational age to within 14.7 days. This accuracy is similar to that of an ultrasound examination in the second trimester of pregnancy. This ability of cfRNA to date the pregnancy is crucial for establishing normal gene-expression

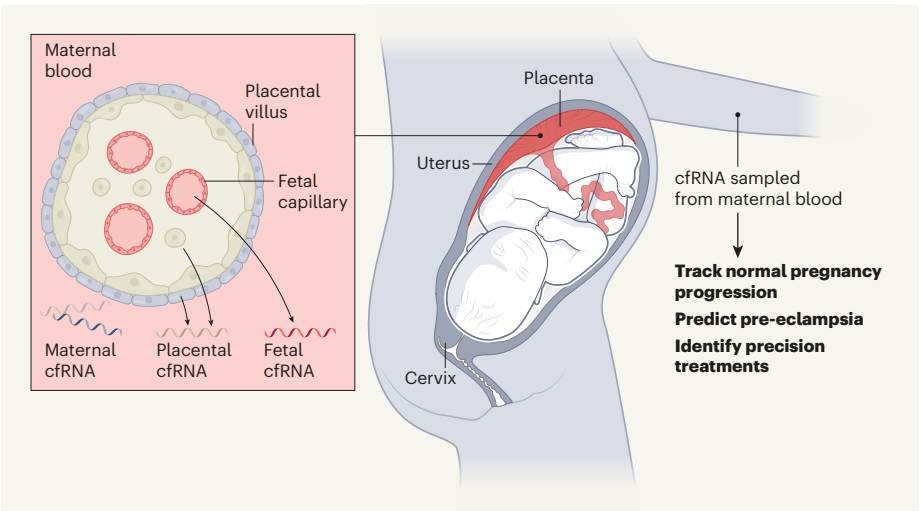

Figure 1 | Applications of cell-free RNA in maternal blood. RNA is released from maternal, fetal and placental tissues, mainly from cells that undergo a programmed form of cell death called apoptosis. Cell-free RNA (cfRNA) transcripts from the fetus can exit from fetal blood vessels (called capillaries) in placental structures called villi, whereas placental cfRNA can enter the maternal bloodstream from the villi and the placental tissues themselves. Once in the maternal bloodstream, the cfRNA transcripts can be sampled using a blood test. By analysing cfRNA in maternal blood, sampled from more than 1,800 pregnant individuals, Rasmussen *et al.*[1] established the normally occurring changes in cfRNA profile at different stages of pregnancy, and generated a model to predict the development of a complication of pregnancy called pre-eclampsia. In the future, alterations in the cfRNA signature that occur in different pregnancy-related disorders could be studied, to predict which drugs might be effective in reversing those gene-expression changes and thus possibly in treating these conditions.

© 2022 Springer Nature Limited. All rights reserved.

signatures at different gestational ages, and the authors suggest that this approach could be an adjunct to pregnancy dating in settings in which prenatal ultrasound is unavailable.

The authors also expand on previous work that demonstrated the potential of detecting fetal-tissue-specific cfRNA in maternal circulation[8]. Rasmussen *et al.* define specific subsets of the cfRNA transcripts in maternal plasma that reflect maternal tissues, fetal organs and the placenta, and generate insights into how these subsets normally change across gestation. Maternal transcriptomes demonstrated increased expression of genes encoding proteins such as collagen that comprise the extracellular matrix, possibly reflecting remodelling of the cervix in preparation for labour and birth. Changes in the abundance of RNA transcripts putatively originating from fetal organs were consistent with known developmental trajectories — for example, levels of transcripts from a part of the fetal kidney that shrinks over time also declined with advancing gestation. These findings demonstrate exciting potential to track pregnancy progression and fetal organ development non-invasively using transcripts in maternal blood.

Next, Rasmussen and colleagues evaluated whether cfRNA signatures in maternal blood during the second trimester could predict the future incidence of pre-eclampsia, well before clinical signs or symptoms develop. The authors compared cfRNA signatures from plasma samples of 72 pregnant individuals who developed pre-eclampsia (cases) with 452 signatures from individuals who did not develop the condition (controls). These samples were taken at an average of 14.5 weeks before delivery. The authors identified seven genes with expression levels that consistently differentiated cases from controls. Four of the genes had previously been associated with either pre-eclampsia or placental development[9–12].

The authors created a mathematical model that used cfRNA signatures to estimate the probability of pre-eclampsia. The model had a sensitivity of 75%, meaning it could identify three-quarters of the eventual cases of pre-eclampsia. In a group of pregnant individuals in which pre-eclampsia occurred in almost 14% of participants, the model had a positive predictive value (PPV) of 32%, meaning that approximately one-third of the individuals who were predicted by the model to develop pre-eclampsia were later diagnosed with the disease. This PPV represents a sevenfold increase compared with the next-most-predictive test for pre-eclampsia currently described in the literature[13]. Notably, the authors found that the predictive capability of the model was not affected by inclusion of maternal race as a variable. This lends further support to abandoning racially biased approaches for diagnosis and treatment that have been found to have little or no utility and that perpetuate racial disparities in health care[14].

A limitation of the authors' work is that the incidence of pre-eclampsia in this group (almost 14%) is higher than the reported global incidence[5] of about 2–8%; thus, the PPV of the test would be lower in groups that have lower rates of the disease. Any future clinical applications would need to consider the benefits gained from early prediction of pre-eclampsia against the potential harms of a possible false positive result, such as unnecessary monitoring or interventions, and increased maternal anxiety.

A key direction for future work will be to determine whether cfRNA that is sampled during the first trimester could be used to detect increased risk for pre-eclampsia, because treatment with low-dose aspirin, the only current preventive therapy for the condition, is likely to be more effective if started before 16 weeks of pregnancy. The wide range of efficacy of low-dose aspirin in preventing pre-eclampsia (estimated to be 2–30% effective)[15,16] highlights the problematic nature of using one treatment for a highly variable disease that manifests in diverse ways. A molecular test that could give insight into the development of pre-eclampsia represents a key step towards a more personalized transcriptomic or genomic approach to pregnancy therapeutics. In addition, transcriptomic data can be entered into computational resources such as the Connectivity Map[17] — an online database of transcriptomic signatures of various cell types after treatment with different therapeutics — to inform the repositioning of existing therapeutics to treat pregnancy-specific diseases.

This large-scale transcriptomic resource from a racially and geographically diverse pregnancy population is exciting for several reasons. Not only have the authors developed a predictive test for pre-eclampsia, but the study's findings also have the potential to provide insights into typical pregnancies and fetal development, and to advance the design of rational, precision therapeutics that can improve pregnancy care.

Lydia L. Shook and **Andrea G. Edlow** are in the Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts 02114, USA, and in the Vincent Center for Reproductive Biology, Massachusetts General Hospital Research Institute, Boston.
e-mail: aedlow@mgh.harvard.edu

1. Rasmussen, M. *et al. Nature* **601**, 422–427 (2022).
2. Edlow, A. G. & Bianchi, D. W. *Biochim. Biophys. Acta* **1822**, 1970–1980 (2012).
3. Fan, H. C., Blumenfeld, Y. J., Chitkara, U., Hudgins, L. & Quake, S. R. *Proc. Natl Acad. Sci. USA* **105**, 16266–16271 (2008).
4. Chiu, R. W. K. *et al. BMJ* **342**, c7401 (2011).
5. ACOG. *Obstet. Gynecol.* **135**, e237–e260 (2020).
6. Stepan, H., Hund, M. & Andraczek, T. *Hypertension* **75**, 918–926 (2020).
7. Ngo, T. T. M. *et al. Science* **360**, 1133–1136 (2018).
8. Koh, W. *et al. Proc. Natl Acad. Sci. USA* **111**, 7361–7366 (2014).
9. Kramer, A. W., Lamale-Smith, L. M. & Winn, V. D. *Placenta* **37**, 19–25 (2016).
10. Schumann, S., Buck, V. U., Classen-Linke, I., Wennemuth, G. & Grümmer, R. *Histochem. Cell Biol.* **144**, 571–585 (2015).
11. Alazami, A. M. *et al. Genome Biol.* **16**, 240 (2015).
12. Cunningham, P. & McDermott, L. *J. Nutr.* **139**, 636–639 (2009).
13. Tan, M. Y. *et al. Ultrasound Obstet. Gynecol.* **52**, 186–195 (2018).
14. Vyas, D. A., Eisenstein, L. G. & Jones, D. S. *N. Engl. J. Med.* **383**, 874–882 (2020).
15. Henderson, J. T. *et al. Ann. Intern Med.* **160**, 695–703 (2014).
16. Van Doorn, R. *et al. PLoS ONE* **16**, e0247782 (2021).
17. Lamb, J. *Nature Rev. Cancer* **7**, 54–60 (2007).

The authors declare no competing interests.
This article was published online on 5 January 2022.

Quantum information

Silicon qubits get closer to achieving error correction

Ada Warren & Sophia E. Economou

A silicon-based quantum-computing platform has met key standards for reducing error — setting the stage for quantum devices that could benefit from established semiconductor microchip technologies. **See p.338, p.343 & p.348**

Quantum bits (qubits) that use the quantum properties of electrons in silicon devices offer enormous potential for developing compact and robust quantum computers that take advantage of the existing silicon-microchip industry. But quantum operations are subject to error, and getting error rates low enough to make quantum silicon devices feasible remains a challenge. Three papers in this issue, by Xue *et al.*[1], Noiri *et al.*[2] and Mądzik *et al.*[3], report demonstrations of qubit operations in silicon devices

© 2022 Springer Nature Limited. All rights reserved.