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Journal Club

"Knowing" Can Be the Medicine for Expecting Mothers

RNA signatures from a single blood sampling during pregnancy can detect a pathologic condition before its onset.

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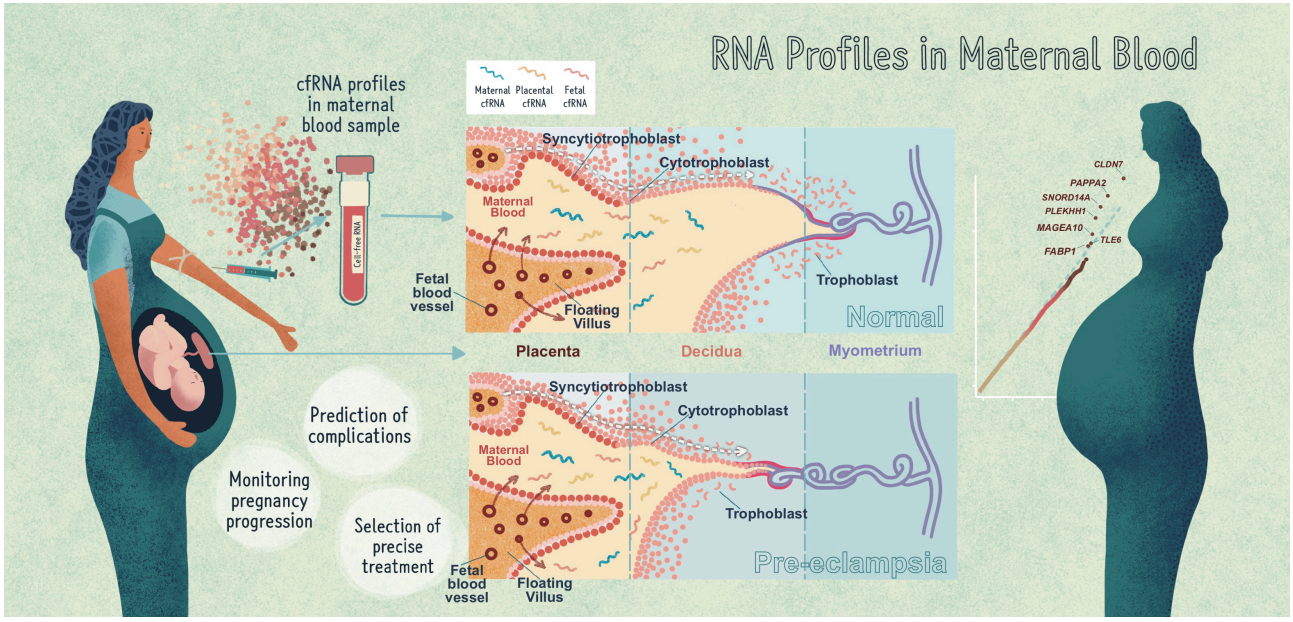

RNA profiles in maternal blood can provide information about pregnancy progression. RNAs originated from placental, fetal, and maternal cells are present in the expecting mother's blood. The cfRNA transcriptome can be constructed from a blood sample, and analyses of the transcriptomes at different pregnancy conditions can establish the specific cfRNA signatures, which can predict certain pregnancy complications such as pre-eclampsia, usually caused by malfunctional placenta. A simple blood test during early pregnancy makes it possible to diagnose pregnancy-related disorders, thereby to help select effective treatments before they become pathogenic.

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Pregnancy carries risks, and even a successful one is difficult. The positive sign of the two lines on a pregnancy test kit doesn't necessarily indicate an easy and smooth experience forthcoming. Expecting mothers undergo significant physical, physiological, and psychological changes that dramatically affect their lives. Losing appetite, feeling nauseous, and even vomiting are very common discomforts, especially in early pregnancy, known as morning sickness, and are also called "ipdeot" in Korean.

While the no-fun-at-all "ipdeot" is usually accompanied with healthy pregnancies, some other complications can bring high risk to the pregnancy. Then, moms-to-be can be anxious; "Am I going to be fine? Is my baby, too?" Due to uncertainty, expectant mothers seek reliable predictions answering whether they and their unborn child will be healthy throughout their gestation period. Although samples from expecting mother's placenta and fetus can be obtained and tested for molecular genetic analyses, it is simply difficult to repetitively reach and collect samples from the placental and fetus' tissues to check their wellbeing throughout pregnancy. In the recently published study, Rasmussen et al. (2022) show that cell-free RNA (cfRNA) transcriptome in pregnant women's blood can be used to predict pre-eclampsia, a condition which can lead to serious complications, months before the illness becomes manifest, independent of other common clinical factors such as age, race, and body mass index (BMI).

Pre-eclampsia is a condition in which pregnant women have high blood pressure induced by a dysfunctional placenta. This pathologic complication develops in 1 in 12 pregnancies worldwide causing damage to other organs, exhibiting various symptoms such as having protein in the urine and swollen limbs, possibly leading to severe illness. Pre-eclampsia is rooted early in pregnancy when the placenta starts to form, but the signs and symptoms are not typically clear until the later stage of pregnancy. Therefore, it is necessary to safely test and monitor to identify and treat those at risk of pre-eclampsia early enough.

Rasmussen et al. (2022) analyzed 2,539 plasma samples drawn from 1,840 pregnancies at various pregnancy stages, from women of multiple ethnicities, nationalities, geographic locations, and socioeconomic contexts. For each sample, they extracted cfRNAs from plasma ranging in volume from ~215 μl to 1 ml, and prepared cfRNA libraries which were then enriched and sequenced. They developed a machine learning model by training and testing their cfRNA data sets, stratified by gestational age. The model's error is equivalent or superior to that with ultrasound-based gestational age, and cfRNA signatures could provide an alternative dating standard for pregnancy. ANOVA indicates that the model is not affected by maternal race, BMI, and age.

Next, they sought to determine whether the maternal plasma cfRNA profiles can assess the molecular status of the placenta, fetal, and maternal organs/tissues. Among transcripts present in expecting mother's blood, there are pregnancy-related sets such as gonadotropin and estrogen hormone pathways. It is notable that seventeen enriched genes originated from mother's olfactory tissues may reflect hypersensitive sense of smell in during pregnancy. They detected changes in fetal gene sets, including those involved in fetal heart development, and progressively increased expression in collagen and extracellular matrix gene sets, indicating expected changes in maternal tissues such as the uterus and cervix during pregnancy. In addition, the identified gene sets were uniquely associated with pregnancy progression. Therefore, the cfRNA profiles from maternal blood samples serve as a non-invasive window into fetal-maternal development.

The authors tested whether the cfRNA signatures during the second trimester (16-27 weeks) predict the development of pre-eclampsia. Pregnant women usually show few symptoms in the second trimester. They performed a case-control study by comparing 72 cases of pre-eclampsia and 452 without. Two-sided Spearman correlation tests identified signatures that separated the cases and controls and consistently identified seven genes linked to pre-eclampsia: *CLDN7*, *PAPPA2*, *SNORD14A*, *PLEKHH1*, *MAGEA10*, *TLE6*, and *FABP1* (Gormley et al., 2017; Ren et al., 2021). The authors also confirmed that the cfRNA signals in the study are independent of both chronic hypertension not caused by the placental disorder and spontaneous preterm birth theorized to share some molecular pathways with pre-eclampsia.

The authors (Rasmussen et al., 2022) invented a machine learning model fed with the cfRNA profiles and used it to estimate the probability of pre-eclampsia. The model had a sensitivity of 75%, which means that it could identify 75% of women who eventually developed pre-eclampsia. It also had a PPV (positive predictive value) of 32%, meaning that about one-third of women who the model positively tagged as being at high risk of pre-eclampsia developed the disease later. This model outperformed another available clinical model based on maternal factors (Tan et al., 2018). Above all, other conventionally considered clinical variables such as maternal BMI, age, and race did not affect the performance of the model, which indicates that the cfRNA signatures can be generally utilized in diverse populations.

The study delivers relieving news that brings exciting possibilities: a single blood sampling early in pregnancy can be used to track pregnancy progression and identify who would be at risk of certain complications before the onset (Attwaters, 2022; Shook and Edlow, 2022). Future directions including utilization of transcriptome tool kits must enhance the diagnostic power during the first trimester. This helps broaden a range of treatment options and reduce false-positive results, leading to unnecessary clinical attention and maternal worries (Durnaoglu et al., 2021; Lee et al., 2021). Science does work and balance, helping wrestle with the situation as the old Korean saying describes: "not-knowing is the medicine and knowing is the disease" (Sanders, 2021).

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CONFLICT OF INTEREST
The author has no potential conflicts of interest to disclose.

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