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Prediction of Preeclampsia by Analysis of Cell-free RNA in Maternal Plasma

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Objective

To analyzed cell-free and cellular RNA in maternal blood and assessed if functional changes of placenta can be evaluated by analyzing cell-free or cellular RNA from maternal blood.

Methods

Three studies

Study 1:

We took 155 blood samples from pregnant women to compare human placental lactogen (hPL) and b-subunit of human chorionic gonadotropin (_hCG) mRNA and protein levels between the cellular and plasma components of maternal blood. To assess clearance of hPL mRNA expression, we obtained blood samples from nine women immediately before and after delivery by caesarean section. mRNA was extracted from the cellular and plasma components of all samples, and hPL and _hCG mRNA expression was analysed by reverse transcription-PCR assay

Study 2:

Data from 62 patients with preeclampsia who were asymptomatic at the time of blood testing and 310 control subjects were analyzed. Multivariable analysis was performed with discriminant analysis.

Study 3:

Case-control study encompassing five women destined to develop PE [cases matched 1:5 for gestational age (GA) with 25 controls]. We measured quantity mRNA expression on tissue samples from chorionic villous sampling (CVS) of normal and PE patients. We then assessed mRNA expressions of vascular endothelial growth factor (VEGFA), VEGFA receptor 1 (Flt-1), endoglin (Eng), placental growth factor (PlGF), transforming growth factor-β1 (TGF-β1), heme oxygenase-1 (HO-1) and superoxide dismutase (SOD). Data were analyzed by nonparametric rank analysis

Result

Study 1:

The concentration of _hCG mRNA in the cellular component positively correlated with the plasma concentration of _hCG protein and _hCG mRNA (p= 0.001 for both).

The concentration of hPL protein in the plasma correlated with the hPL mRNA concentration of the cellular component (p,0.05). For both hPL and _hCG, the mRNA concentration of the cellular component was greater than that of the plasma component (22.9-fold higher for hPL and 4.3-fold higher for _hCG). The half life of hPL mRNA clearance was significantly longer for the cellular fraction (mean half life=203.8 min, range 150–3465 min) than for the plasma fraction (mean half life=32.2 min, range 15–385 min) (p=0.008).

This findings indicate that the concentration of hPL and _hCG mRNA is significantly higher in the cellular component of maternal blood samples than in the plasma component. Cellular mRNA in maternal blood is useful for non-invasive evaluation of placental function.

Study 2:

Uni variable analysis identified vascular endothelial growth factor receptor 1 as the marker with the highest detection rate; placenta- specific 1 with the

lowest. Mean estimated score for preeclampsia was 9.4 for control subjects and 72.5 for subjects who experienced preeclampsia. A receiver operating characteristic curve that was obtained with the estimated score for preeclampsia as a test variable yielded a detection rate of 84% (95% CI, 71.8-91.5) at a 5% false-positive rate with an area under the curve of 0.927 (P <.001). Again, detection rate and score for each patient that classified as preeclampsia also correlated with its severity.

A panel of messenger RNA is able to detect subjects who will experience preeclampsia.

Study 3:

For all the mRNA species considered in this study, all the mean observed ranks in the PE group were significantly altered compared to the rank expectation among controls. mRNA for Eng and TGF-β1 were the markers with the highest degree of aberration in PE, in respect to controls. The results are consistent with those already reported for the corresponding circulating proteins. mRNA for HO-1 and SOD were instead associated with the lowest aberration.

It is assumed that the pathogenesis of PE is associated with pathophysiological alterations of trophoblasts in early gestation. Our study has directly proved that gene expressions relating to angiogenesis or oxidative stress are altered in the first trimester trophoblasts that go on to develop PE later. These results would put the basis for a possible screening method for PE by using residual CVS

Conclusion

1. Alteration of mRNA expressions of cell-free and cellular RNA in maternal blood reflects placental pathophysiological alterations associated with preeclampsia.
2. Using analysis of cell-free and cellular RNA in maternal blood, prediction of preeclampsia is feasible with high detection rate.
3. In cases that develop preeclampsia at later gestation, pathophysiological alterations in the placenta have already started at 11 weeks.
4. First trimester prediction of preeclampsia may be feasible by analyzing cell-free or cellular RNA in maternal blood.

Keywords: Cell free mRNA, prediction preeclampsia