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Searching for New Biomarkers for Pre-eclampsia: Is there a Role for Corin?

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Johannes J. (Hans) Duvekot[1] and Jeanine E. Roeters van Lennep[2]*
[1]Department of Obstetrics and Gynecology, Erasmus University Medical Centre, Rotterdam, the Netherlands
[2]Department of Internal Medicine, Erasmus University Medical Centre, Rotterdam, the Netherlands

Pre-eclampsia (PE) is still one of the most important causes of maternal morbidity and mortality worldwide. The pathogenesis of PE remains obscure due to its heterogeneous, multi-systemic nature. Various theories have been put forward to explain the pathogenesis and involve genetic predisposition, immune system dysregulation, placental ischemia and inflammation. At present, failure of adequate trophoblastic invasion in the maternal spiral arteries and spiral artery remodeling remains the most promising explanation. The pathophysiological event crucial to the development of the resulting clinical disease is generalized endothelial dysfunction [1].

Since placentation including this trophoblastic invasion starts very early in pregnancy, biochemical markers are expected to be altered before the onset of clinical disease, which by definition begins during the second half of pregnancy. Effective methods for the prevention of PE are still lacking but early prediction could be beneficial for appropriate antenatal surveillance and prevention of maternal and fetal complications. The only effective treatment of PE is delivery of the fetus and placenta. The hope is that identification of pre-clinical biomarkers for the disease might also help to develop alternative strategies for treatment.

In the quest for sensitive biomarkers for early prediction of PE recent research has been focused on identification of specific predictive biomarkers. Most of those biomarkers focus on the associated anti-angiogenic and angiogenic factors [2].

Another group of biomarkers could be related to volume homeostasis and blood pressure regulation. In uncomplicated normotensive pregnancies total blood volume and especially plasma volume increases with approximately 40%. In preeclamptic pregnancies plasma volume shows an attenuated increase. In previously preeclamptic women, plasma volume was also found to be significantly smaller in the non-pregnant state.

The events that lead to volume expansion in pregnancy, although not completely understood, are most likely triggered by an early primary fall in systemic vascular tone [3]. This acute fall in vascular tone of the arterial and venous system takes place at the time of or shortly after nidation. The 'underfill state' that results from this vasodilatation leads to an activation of several volume-retaining mechanisms. One of those mechanisms is mediated by natriuretic peptides. During the clinical phase of PE atrial natriuretic peptide (ANP) levels are increased [4].

Corin (also known as atrial natriuretic peptide-converting enzyme) is a cardiac protease that activates ANP, a cardiac hormone that not only regulates blood volume but indirectly also blood pressure. Unexpectedly, corin expression was also detected in the pregnant uterus. In experiments with corin- and ANP knockout mice, they developed hypertension and proteinuria during their pregnancies [4]. Spiral arteries in knockout animals were smaller and less abundant suggesting a direct impact upon spiral artery remodeling. Analysis of the placental implantation sites in these mice indicated that trophoblast invasion was markedly impaired when compared with the wild type. It may be concluded that uterine corin seems to play an essential role in early placentation. However, during human pregnancy both corin and ANP levels become increased and during preeclamptic pregnancies these levels are even more increased. Moreover, missense mutations in the corin gene were identified in preeclamptic women [5].

The present study of Liu et al. in this issue [6] showed that serum soluble corin

***Corresponding author:** Jeanine E. Roeters van Lennep, Department of Internal Medicine, Erasmus University Medical Centre, PO Box 2040, 3000 CA Rotterdam, The Netherlands, E-mail: j.roetersvanlennep@erasmusmc.nl

was already increased in mid-pregnancy in women who later in pregnancy developed hypertensive disorders of pregnancy [6]. This association of increased levels of serum corin in combination with hypertensive disorders of pregnancy was previously also found in other studies. The study by Khalil et al. [7] showed increased levels of corin during the first trimester, 4-6 weeks earlier than in the study by Liu et al., in women who eventually developed early preeclampsia.

The question now is, is corin an early marker of PE and is the increase in corin levels a physiological reaction to an increase in blood pressure, if so increased corin levels could be the consequence of the attenuated increase in plasma volume. On the other hand, is it possible that there is a low corin expression in very early pregnancy as a physiological reaction to the relative 'underfill state', which in its turn leads to defective placentation.

A possible answer to these questions could be found in the different origin sites of corin. In very early pregnancy low uterine corin may cause impaired trophoblast invasion and when pre-eclampsia eventually occurs or is starting to occur corin derived from the heart is upregulated leading to increased ANP levels. Whether formerly preeclamptic women that initially have a smaller plasma volume, have lower corin levels or expression is not known.

In conclusion, the regulation of the natriuretic peptides during pregnancy is worthwhile to investigate more thoroughly and offers fascinating new opportunities in the search for good biomarkers for PE.

Irrespective of the cause, early recognition of increased corin levels in human pregnancy is promising as predictor of PE. The large interindividual differences in serum levels makes this biomarker still not suitable for its use in individual patients.

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