Precursors to pre-eclampsia: are there markers in the fetal circulation?

Annemarie HENNESSY
Department of Renal Medicine, Royal Prince Alfred Hospital, Missenden Rd, Camperdown, NSW 2050, Australia

One of the fundamental issues in pre-eclampsia (hypertension in pregnancy) research is to find serum proteins that can act as markers of disease predisposition, remote disease onset, imminent disease onset or disease activity at the height of its destructive powers. We make assumptions, not infrequently, that positive findings at the time of delivery reflect early changes in the maternal and fetal circulations. Very little has been defined in terms of fetal circulation, as it is, by and large, deemed to be harder to access and less likely to lend itself to useful non-invasive diagnostic tests in early pregnancy. The study published in this issue of Clinical Science by Prickett et al. shows that there is a differential expression of the precursor molecule of CNP (C-type natriuretic peptide), N-terminal proCNP, in pre-eclampsia. At term, pre-eclamptic umbilical cord plasma concentrations are decreased relative to normal pregnancy, possibly reflecting a decrease in placental production. At the same time maternal levels are increased relative to normal pregnancies and this possibly reflects an increase in myometrial/endovascular production. There is no doubt that the predominant actions of these hormones are local and whether plasma levels are a true reflection of dynamic changes in local production and effect is yet to be seen. This study represents a promising start in identifying large stable molecules which could be markers for pre-eclampsia. This study has relatively small numbers of patients and work still needs to be done to determine the utility of umbilical cord levels in early phases of the disease. Whether serum levels of N-terminal proCNP can provide an accurate reflection of normal or pathological maternal uterine adaptation to pregnancy remains a question worth evaluating.

Endothelial dysfunction has been recognised as the central unifying pathological process which explains the features of pre-eclampsia: proteinuria, hypertension, liver dysfunction, cerebral oedema and renal failure in human pregnancy [1]. Investigations have streamed into two channels: attempts to find the cause of the placental dysfunction in the first instance (stage 1) and attempts to find the factor arising from placentas that causes the maternal endothelial reaction (stage 2) [2]. Markers of this endothelial reaction have included fibronectin [3], endothelin/nitric oxide [4] and, recently, sFlt-1 [5]. Whether these factors can reliably be shown to be elevated prior to the onset of the disease is yet to be determined. Whatever the placental or endovascular mediators, there is an imbalance of vasodilators and vasoconstrictors, which lead to the development of maternal hypertension.

Tissue effects of the vasodilator and antimitotic peptide CNP (C-type natriuretic peptide) have been identified in pre-eclampsia. There is a decrease in placental and an increase in myometrial levels compared with normal pregnancy outcomes [6]. Disappointingly, this has not been evident in blood concentrations of CNP in patients with the disease [7].

The study by Prickett et al [8], in this issue of Clinical Science has identified that fetally-derived factor and placental or maternal decidual levels of CNP precursors exhibit a paradoxical gradient in pre-eclampsia compared with normal pregnancy. There is relatively more proCNP in the maternal circulation in

Key words: C-type natriuretic peptide (CNP), fetal circulation, N-terminal proCNP, pre-eclampsia, pregnancy.

Correspondence: Professor Annemarie Hennessy (e-mail ahennese@renal.rpa.cs.nsw.gov.au).

© 2004 The Biochemical Society
pre-eclampsia and relatively less in the fetal circulation. In both normal and disease states, there was a greatly elevated fetal concentration of N-terminal proCNP compared with the maternal circulation. The authors [8] postulate that these gradients indicate that vascular-derived factors are pathologically changed with altered endothelial vasodilator function and potentially altered mitotic activity. The other fundamental assumption of their study is that the larger, more stable, pro molecule is a better representative of the tissue CNP effect than the daughter compound CNP.

Prickett et al. [8] raise the possibility of this test as a marker of pre-eclampsia, although they concede that a gestation-specific effect and the effect of lower birth weight need to be considered in any analysis of the biological significance of the results. It could be argued that consideration of other maternal factors, such as smoking [9] and mode of delivery, need to be accounted for in any analysis of pre-eclampsia and endothelial markers.

Although there are limitations in interpreting a study of small numbers of patients, this study [8] at least attempted to differentiate relatively mild disease from normal. Whether the test would be useful in women with severe disease has not been determined, but there is likely to be profound differences in women with severe disease. Application of test results to the vast majority of women who need to be differentiated between gestational hypertension and pre-eclampsia is a much more vexing question. The capacity to differentiate a mild increase in blood pressure from women with impending widespread endothelial dysfunction is an important goal.

Whether the loss of the vasodilator CNP in the fetal circulation and an increase in the maternal circulation will be a useful predictive measure or diagnostic measure is yet to be seen. This study [8] represents a promising start in identifying large stable molecules which could be markers for pre-eclampsia. This study has relatively small numbers of patients and work still needs to be done to determine the utility of umbilical cord levels in early phases of the disease. Whether serum levels of N-terminal proCNP can provide an accurate reflection of normal or pathological maternal uterine adaptation to pregnancy remains a question worth evaluating.

REFERENCES