Circular RNA and pre-eclampsia: on the long road from the laboratory to the bedside

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Linked article: This is a mini commentary on Y-G Zhang et al. To view this article visit http://dx.doi.org/10.1111/1471-0528.13897.

Most practicing obstetricians and gynaecologists are probably unaware of the existence of circular RNAs (circRNAs). These are single-stranded RNA molecules produced by a variety of post-transcriptional processes, which subsequently become circular. Although details of the possible functions of circRNAs are unknown, these molecules may be involved in cardiovascular, neurological and neoplastic disorders, and may be potential biomarkers for some of these diseases (Qu et al. *Cancer Lett* 2015;365:141–8).

In this article, Zhang et al. (*BJOG* 2016;DOI: 10.1111/1471-0528.13897) report for the first time that the concentration of a specific circRNA in the cellular component of maternal blood was higher in a group of pregnant women who subsequently developed pre-eclampsia than in control women. This observation opens a new scenario in the field of pre-eclampsia prediction. However, as acknowledged by the authors, this study has several limitations and must be considered a pilot and the findings must be considered preliminary. Despite efforts to make the predictive model robust, the small study population did not permit the assessment of the predictive efficacy of circRNA in relation to gestational age. First, the 8- to 20-week window for blood sampling used in the study is clinically very large. Second, there are different phenotypes of pre-eclampsia. Furthermore, it is a long way from the demonstration of differences in circRNA concentrations between pregnancies destined to develop pre-eclampsia and uncomplicated control women to the clinical use of this biological feature for effective prediction and screening for pre-eclampsia. In addition, several more validation steps would be required before circRNA could be considered a clinical tool for pre-eclampsia prediction. (Prefumo et al. *BJOG* 2015;122:904–14; Kleinrouweler et al. *Am J Obstet Gynecol* 2016;214:79–90.e36).

Finally, from a biological standpoint, the current study tells only part of the story: the detection assay used was not sufficiently sensitive to investigate free circRNA concentrations in maternal plasma or serum, whose quantitative and qualitative composition is likely to be significantly affected by the presence of the fetus and placenta (Koh et al. *Proc Natl Acad Sci USA* 2014;111:7361–6). It will also be important to further characterise the differential expression of circRNA in the different subpopulations of cells found in the maternal blood to place this new finding in a more comprehensive pathophysiological and clinical perspective.

In conclusion, circRNAs represent promising biomarkers for pre-eclampsia; however, the available evidence is insufficient to tell us whether circRNA-based tests will eventually make it to the bedside.

Disclosure of interests

Full disclosure of interests available to view online as supporting information. ■