



The placenta is the villain or victim in the pathogenesis of pre-eclampsia

AGAINST: The pre-eclamptic placenta: a victim of maternal cardiovascular dysfunction

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Pre-eclampsia is a disease whose characterisation has not changed since the cluster of signs associated with the disorder were first described 150 years ago. In Professor Murthi's own words from a recent publication in 2020, she states: 'It is hypothesized that the pathophysiology of early-onset pre-eclampsia has its origins in the placental and uterine vasculature, where inadequate vascular remodelling leads to repeated ischemic-reperfusion events within placental tissue' (Ellery *et al. Int J Mol Sci.* 2020;21:806). When even a placental biologist seems unsure of the aetiology of this placental disorder, it comes as no surprise that pre-eclampsia has earned the moniker 'disease of theories'. Such theories predominate because researchers have failed to provide biological mechanisms relating the clinical epidemiology of pre-eclampsia to observed cellular and organ dysfunction.

All the evidence cited to support the placenta's role in pre-eclampsia is not in question – it is self-evident to most clinicians and academics that the placenta is central in the pathophysiology of pre-eclampsia. However, the putative aetiological role for the placenta in pre-eclampsia is questionable when one considers that both villous and vascular histological placental lesions are neither sensitive or specific for pre-eclampsia, with the overall prevalence of these

lesions being higher in placentae from uncomplicated than pre-eclamptic gestations (Falco *et al. Ultrasound Obstet Gynecol.* 2017;50:295–301). Surely, a re-evaluation of the evidence is required for a condition that still claims the lives of approximately 60 000 women each year worldwide. An emerging alternative hypothesis is that poor trophoblast development and placental dysfunction may result from maternal cardiovascular dysfunction rather than the other way around (www.youtube.com/watch?v=9_wszfCNqqM) (B. Thilaganathan. Accessed 7 September 2020; open access).

Pre-eclampsia and cardiovascular disease share similar risk factors (age, obesity, diabetes, chronic kidney disease) and pre-existing cardiovascular disease is the strongest risk factor (chronic hypertension, congenital heart disease) for the development of pre-eclampsia. There is now abundant evidence from peripheral waveform analysis (uterine, radial and ophthalmic artery Doppler), maternal echocardiography and angiogenic marker studies that maternal cardiovascular dysfunction precedes the development of pre-eclampsia by several weeks to months. Importantly, cardiovascular signs and symptoms predominate (hypertension, cerebral oedema, stroke) in pre-eclampsia and persist in the postpartum period where the legacy is a chronic hypertension rate of 30% in the decade

following birth (Thilaganathan. *Hypertension* 2020;76:321–2; Thilaganathan *et al. Hypertension* 2019;73:522–31). Given these findings, it is no surprise that most pre-eclampsia prevention strategies employ cardiovascular drugs (aspirin, calcium, statins, metformin and antihypertensives).

Placenta malperfusion caused either by suboptimal maternal cardiovascular performance or as a result of excessive pregnancy demand may lead to pre-eclampsia following exactly the same translational mechanisms previously described. Despite the seriousness of the maternal and fetal consequences of pre-eclampsia, we have still to develop effective screening, a reliable diagnostic test, effective therapy or amelioration of the postpartum maternal cardiovascular legacy. These will only become available when academics and clinicians shed the veneer of confirmation bias and accept the strong arguments for the cardiovascular aetiology of pre-eclampsia.

Disclosure of interests

None declared. A completed disclosure of interest form is available to view online as supporting information. ■