Re: Pre-eclampsia is primarily a placental disorder

The arteriolar injury in pre-eclampsia

Sir,
Verlohren and Thilaganathan use the historical language of ‘failures of deep trophoblast invasion’ and ‘incomplete spiral artery re-modelling’ in their recent BJOG debate over the aetiology of pre-eclampsia.\(^1,2\) Dr Verlohren says that ‘the first hit leading to abnormal placentation is still unknown’. Prof. Thilaganathan notes that ‘over 80% of pre-eclampsia cases occur at term, where the prevalence of a small-for-gestational-age fetus is only 15%’ casting some doubt over the placental origins of the condition. We believe that these observations can be reconciled in the ‘uterine reinnervation view’ of pre-eclampsia, as recently described in the BJOG since 1902 series;\(^3\) however, we add further, new observations to support that view (Figure 1A–D).

Dr Verlohren’s ‘primary hit’ to the uterus is a prepregnancy injury to uterine vasomotor nerves affecting both the placental bed and extra-placental myometrium, caused primarily by physical efforts during defecation, and uterine evacuation, but also previous hypertension (Figure 1A, C, D). Different patterns of perivascular hyalinisation around narrowed arterioles indicate different patterns of injury to the arterioles, including that from prior hypertension (Figure 1C). Release of cytokines and growth factors from injured nerves leads to regenerating nerve fibres and hyperplasia of denervated arterioles that express abnormal purinergic, P2X3, ‘stretch’ receptors (Figure 1B), though not in their terminal branches (Figure 1D).\(^4\) Importantly, these ‘stretch’ receptors are also found in extra-placental myometrium, which we believe may account for the development of ‘late-onset’ pre-eclampsia (Figure 1B). Stretching these purinergic channels activates a renal, cortico-medullary vascular shunt that results in hypertension and proteinuria, among other cardiovascular adjustments.\(^5\) Stretching injured tissues may release many maternal proteins, e.g. s-flt-1, placental growth factor and tyrosine kinase, which may bear some relationship to disease activity but are not central to the mechanism of pre-eclampsia.\(^1,2\)

Many of the cardiovascular changes in pre-eclampsia may result from autonomic adjustments through viscerovisceral mechanisms, e.g. uteroenral, cardioenral, hepatoenral, lienorenal, etc. described by Professor KJ Franklin, FRS in the 1950s that are readily demonstrable using standard, Doppler techniques.\(^5\)

Figure 1. The aetiology of injuries to uterine arteries in pre-eclampsia. (A and C stained with haematoxylin & eosin; B and D stained with anti-P2X3). (A) Hyperplasia of the tunica media in injured uterine arteries in pre-eclampsia with limited perivascular hyalinisation (×100); (B) the same field stained with anti-P2X3 to demonstrate purinergic (P2X3) ‘stretch’ receptors in injured uterine arterioles [that may contribute to ‘early-onset’ (<34 weeks) pre-eclampsia] and extrapolacental myometrium [that may contribute to ‘late-onset’ (>34 weeks) pre-eclampsia] (×100); (C) serial layers of perivascular hyalinisation (‘basket-weaving’) in a woman with pre-existing hypertension who developed superimposed pre-eclampsia at 37 weeks of gestation (×200); and (D) a similar field stained with anti-P2X3 confirms perivascular hyalinisation without evidence of purinergic stretch receptors in small arterioles in placental villi (×200).
The nature and extent of the cardiovascular changes suggest that we may need to deliver pre-eclamptic women sooner to avoid fixed injuries to renal arterioles that precede hypertension in later life.

References

1 Verlohren S. Pre-eclampsia is primarily a placental disorder: FOR: Pre-eclampsia is primarily a placental disorder. BJOG 2017;124:1762.

2 Thilaganathan B. Pre-eclampsia is primarily a placental disorder: AGAINST: Pre-eclampsia: the heart matters. BJOG 2017;124:1763.


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