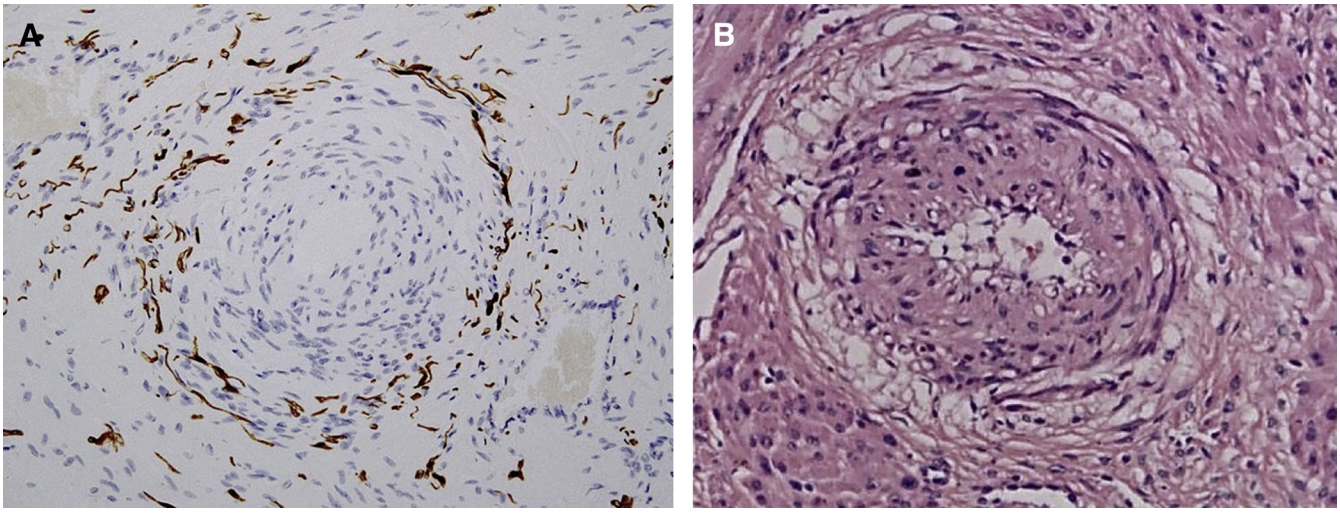
Progressive uterorenal denervation may contribute to both placental and cardiovascular syndromes?

TO THE EDITORS: Cain et al[1] find that women experiencing "placental syndromes" are at increased risk of serious cardiovascular disease within 5 years. We believe they have a common source of injury, namely, progressive autonomic denervation. Both uterus and kidneys receive sympathetic nerves from the same thoracic segments (T10-12). Persistent physical efforts during defecation are a common source of progressive autonomic injury in Western populations where they complicate 20-30% of Western bowel movements.[2] With the introduction of Western fast foods and removal of squat toilets over the past 25 years, it is becoming a major source of recent, cardiovascular morbidity in China.[3]

In terms of the obstetrics syndromes, stretching injured, intrauterine vasomotor nerves (Figure) may activate uterorenal nerves to create a renal corticomedullary shunt leading to preeclampsia with, or without, intrauterine growth restriction.[4] Disruption of narrowed uterine arterioles may cause placental abruption and denervation anywhere in the lower genital tract may increase the risk of opportunist infection and preterm birth, although this may be a less specific outcome compared to early-onset preeclampsia.[4] Hypertension is a common antecedent to the listed, cardiovascular syndromes.[1] The histological hallmark of "resistant" hypertension is renal arteriolar sclerosis that has strikingly similar features to the uterine lesion (Figure, A). Resistant renal hypertension may result from similar mechanisms, namely injury to renal nerves caused by downward displacement of the kidney through persistent physical efforts during defecation, though clearly, there may be many other contributory factors to hypertension including increased body mass index, persistent hyperglycemia, and type 2 diabetes. By excluding preterm labor and intrauterine growth retardation from their definition of the placental syndromes, Cain et al[1] may trade some sensitivity for specificity. Nevertheless, they present a compelling argument for short-term follow-up of women with placental syndromes in their population. These women may also be at risk of

FIGURE
Neurovascular etiology of many obstetric and gynecological syndromes



A, Gynecological lesion demonstrates halo of injured nerves around circumference of injured arteriole with irregular hyperplasia of vessel wall. This lesion occurs in many painful, premenstrual gynecological syndromes. Injuries to vasomotor nerves result in release of cytokines with regeneration of injured nerves and hyperplasia of now-denervated vessel walls. **B**, Obstetric lesion demonstrates halo of hyalinization around circumference of narrowed arteriole with irregular hyperplasia of tunica media and intima. Injured nerves cannot extend to placental bed during pregnancy. This lesion bears close resemblance to renal arteriolar hyperplasia where displacement of kidney by up to 2 vertebral bodies about its neurovascular pedicle may lead to similar injuries and appearances.

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gynecological problems and other Western diseases associated with injuries at different levels of the branches of the sympathetic chains that have longer latent periods between neural injury and clinical presentation.[5]

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REPLY

The authors thank Quinn for comments regarding our article titled "Pregnancy as a window to future health: maternal placental syndromes and short-term cardiovascular outcomes."[1] The article presented the short-term risk of cardiovascular disease among nulliparous women experiencing placental syndromes. We then further evaluated this risk when the women experienced placental syndromes in conjunction with a preterm delivery or delivery of a small-for-gestational-age (SGA) infant. A statewide, multiyear maternal-infant database in the state of Florida provided data for our study. Due to the nature of the study database and the reliance primarily on administrative diagnostic coding, we were unable to identify the root cause of subsequent cardiovascular disease among these women. Although the placental syndromes may be the unmasking of underlying disease, the syndrome itself may also cause damage that increases a woman's lifetime, and even shorter term, risk of cardiovascular disease. Dr Quinn's letter to the editor adds to the possible etiologies for subsequent cardiovascular disease; specifically discussing the potential stretching of intrauterine nerves leading to uterorenal nerve activation and preeclampsia. These vascular changes may then cause resistant renal hypertension and ultimately cardiovascular disease. Prior studies note vascular dysfunction may be caused by preeclampsia.[2,3] Certainly, further investigation into the pathophysiology of placental syndromes and their impact on vascular disease is warranted.

Dr Quinn also notes a trade of sensitivity for specificity in our decision to not include intrauterine growth restriction and preterm labor in our definition of placental syndromes. In an effort to evaluate the additional impact of poor fetal growth and preterm deliveries, we included SGA and preterm birth in addition to placental syndromes. Women who experienced a placental syndrome as well as either SGA or preterm birth were at greater risk of cardiovascular disease than those with a placental syndrome without SGA or preterm birth (Table 2).[1] We agree that, if we were to have omitted consideration of SGA and preterm birth from the study entirely, our definition of placental syndromes would have had suboptimal sensitivity. We instead chose to highlight this increase in risk conferred by SGA and/or preterm birth by evaluating these outcomes both with and without a more specific definition of placental syndromes.

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