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Barbara T. Alexander

Hypertension during pregnancy when associated with new-onset proteinuria is termed "preeclampsia."1,2 Preeclampsia is thought to initiate with improper remodeling of the uterine spiral arteries leading to reduced placental/fetal perfusion and subsequent extensive dysfunction of the maternal vascular endothelium.1,2 Reduced placental perfusion, however, may not always result in preeclampsia.3 Additionally, reduced placental perfusion may not necessarily reflect an imbalance between nutrient delivery and the metabolic needs of the fetus. Nonetheless, based on the fact that low placental perfusion is not always associated with preeclampsia, Roberts and Gammill1 proposed that the maternal response to reduced placental perfusion requires interaction with pre-existing maternal factors. Maternal factors that may contribute to increased maternal susceptibility to reduced placental perfusion and development of preeclampsia or hypertensive disorders of pregnancy include genetic, behavioral, and environmental factors.1

Numerous studies indicate that a genetic component may contribute to increased risk for preeclampsia and hypertensive disorders of pregnancy.1,3,4 Women and men born to a woman with preeclampsia are at greater risk for developing, or fathering, a preeclamptic pregnancy, suggesting transmission of a fetal gene for increased susceptibility to preeclampsia.3,4 However, this susceptibility is greater in women than in men, suggesting passage of maternal susceptibility genes from mother to daughter in addition to fetal susceptibility genes.3,4

Behavioral and environmental risk factors for preeclampsia include obesity, hypertension, and type 2 diabetes1,5; all of these are risk factors for development of cardiovascular disease and are characterized by endothelial dysfunction.6 Cardiovascular disease, including hypertension, is thought to result from genetic and environmental factor interactions. Recent epidemiological studies report an inverse relationship between weight at birth and blood pressure, suggesting that influences in the prenatal environment that slow fetal growth may also modulate postnatal patterns of gene expression leading to increased risk for cardiovascular disease in later life,7 an observation strongly supported by animal studies.8–10 Reduced perfusion to the placenta and fetus is one insult that can permanently alter or "program" both the structure and physiology of the fetus.7–10 Postnatal stress may exacerbate the prenatal effects of programming and contribute to development of obesity, hypertension, and type 2 diabetes.7,8,10

Although reduced placental perfusion may result in intrauterine growth restriction, the maternal response does not always result in preeclampsia.1 Thus, intrauterine growth restriction in a normotensive pregnancy suggests that the maternal response to reduced placental perfusion is absent, indicating a lack of susceptibility genes, either fetal and/or maternal, and a lack of maternal behavioral or environmental risk factors. In this issue of Hypertension, Rasmussen and Irgens11 report that women born small after a normotensive pregnancy are more likely to develop preeclampsia and hypertensive disorders of pregnancy. Moreover, Rasmussen and Irgens11 report that fathers born small are not associated with their partner’s risk for development of preeclampsia and hypertensive disorders of pregnancy. Therefore, although a genetic component cannot be ruled out, it is unlikely that susceptibility genes, either of fetal or maternal origin, contribute to the increased risk for women born small from a normotensive pregnancy to develop preeclampsia or hypertension in their own pregnancies.

Endothelial dysfunction is observed in both children and adults born small7; endothelial dysfunction is also observed in animal models of reduced uterine perfusion and fetal malnutrition.7,8,10 Germain et al,12 report that maternal endothelial dysfunction may contribute to placentation-related defects, such as pre-eclampsia. Therefore, pre-existing maternal endothelial dysfunction may serve as a link between reduced placental perfusion and the maternal response.1,12 Because endothelial dysfunction is a reported consequence of being born small, it may serve as the link between reduced placental perfusion and the increased risk for development of preeclampsia and hypertensive disorders of pregnancy in women born small. Therefore, adverse consequences of reduced placental perfusion may lead to prenatal induced alterations in endothelial function in women born small, enhancing not only their risk for development of cardiovascular disease in later life but also their risk for development of preeclampsia and hypertensive disorders of pregnancy. Confounding behavioral and environmental factors derived from health consequences of obesity, type 2 diabetes, and cardiovascular and renal disease are all risk factors for individuals born small.7 The presence of these confounding factors may exacerbate maternal susceptibility to reduced placental perfusion and development of pregnancy-induced hypertension and preeclampsia in women born small. However, within the study...
According to Roberts and Gammill,1 manifestation of the maternal disorder of preeclampsia requires initiation by reduced placental perfusion, followed by a maternal response that occurs only in the presence of confounding maternal factors (genetic, behavioral, or environmental). Preeclampsia is associated with reduced perfusion, not only to the placental/fetal unit, but to all maternal vascular beds and organs, suggesting that pre-existing maternal endothelial dysfunction could serve as a confounding maternal factor. Reduced placental perfusion resulting in fetal undernutrition can lead to intrauterine growth restriction and subsequent permanent adaptive changes, such as endothelial dysfunction. Thus, in women born small of normotensive pregnancies, pre-existing endothelial dysfunction programmed by their in utero exposure to reduced placental perfusion may contribute to their increased risk for development of pregnancy-induced hypertension or preeclampsia.

Adverse prenatal influences can have long-term effects contributing to cardiovascular disease. There is now evidence to suggest that, in women, prenatal insults may also contribute to their risk for development of hypertensive disorders of pregnancy. Thus, prenatal origins of endothelial dysfunction may initiate susceptibility and enhance the maternal response to improper vascular remodeling, resulting in pregnancy-induced hypertension.

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None.

References