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Preeclampsia and Prematurity as Precursors to Adolescent Obesity

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It has been recognized for nearly 70 years that the early environment in which a child grows and develops could have long-term effects on subsequent health and survival.[1,2] The period from conception to birth is a time of rapid growth, cellular replication and differentiation, and functional maturation of organ systems. These processes are very sensitive to alterations in the intrauterine milieu. The Barker hypothesis proposes that the fetus adapts to an adverse intrauterine milieu by optimizing the use of a reduced nutrient supply to ensure survival. However, although the adaptations may aid survival of the fetus, they become a liability in situations of nutritional abundance.[2]

Small-for-gestational-age infants have a reduced body fat mass at birth, but then develop a relative increase in body fat mass during childhood, and go on to have higher visceral fat mass during childhood and adult life.[3,4] The landmark cohort study of 300 000 men by Ravelli et al showed that exposure to the Dutch famine of 1944-45 during the first one-half of pregnancy resulted in significantly higher obesity rates at age 19.[1]

Most of the studies in the field of developmental programming of adult disease have focused on small for gestational age term infants and their increased risk for the later development of cardiovascular disease and or type 2 diabetes. Prematurity even in the face of normal fetal growth may also predispose the individual to develop increased adiposity and insulin resistance later in life.[5] However, other studies fail to show an association between prematurity and the later development of obesity in childhood. In a large study of over 800 children in the Infant Health and Development Program in Norway, 8-year-old children whose birth weights were ≤1500 g at birth were significantly less likely to be obese.[6] In a smaller study (The Helsinki Study of Very Low Birth Weight Adults) of 116 preterm infants with birth weights of <1500 g, there was no difference in percent fat mass at 22 years of age between very low birth weight and term. Thus, it remains to be determined whether prematurity per se may result in increased adiposity in later adulthood.

In this issue of *The Journal*, Washburn et al[7] have identified yet another population at risk for the later development of obesity—preterm offspring of mothers with preeclampsia.

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Previous studies have shown that term offspring of women with preeclampsia have a modest increase in body mass index (BMI). Washburn et al have now found that prematurity potentiates the increased adiposity. Of note, the differences in adiposity measures between offspring of normotensive and preeclamptic mothers persisted after adjustment for race, antenatal steroid exposure, and maternal BMI. Increased adiposity was not related to decreased aerobic fitness or increased caloric intake at 14 years of age. Surprisingly, increased adiposity was only observed in male offspring. BMIs of female offspring of women with preeclampsia did not differ from offspring of normotensive women. In contrast, a recent systematic review of 8 studies of term infants compared BMI with data on 39 611 participants.[8] In 5 studies, BMI was greater in exposed individuals, but this finding was significant only in 2, and then only in girls in 1 study and boys in the other study. Significant increases in BMI were seen both when female individuals were considered alone and in studies considering male individuals alone. The sex differences in outcome between the 2 studies may be due to the fact that only 40% of the cohort was able to be followed into adolescence. Additional studies will need to be performed to conclude that there are truly sex differences in outcome in the preterm population exposed to maternal preeclampsia.

The mechanisms underlying the development of increased adiposity in the male offspring remain to be determined. Possibilities include increased leptin production by the placenta as the authors discuss. In addition, oxidative stress and mitochondrial dysfunction may also play a role. A number of studies have shown that preeclamptic pregnancies are associated with oxidative stress in the newborn (reviewed in reference[9]). Oxidative stress and mitochondrial dysfunction are associated with obesity, although it is controversial as to whether mitochondrial dysfunction actually drives the development of obesity or whether obesity causes mitochondrial dysfunction (reviewed in reference[9]).

It is now evident from multiple studies including Washburn et al that children and young adults born to mothers with preeclampsia either at term or preterm are at risk for developing obesity later in life. Thus, these children need to be carefully monitored and may benefit from early interventional strategies to prevent the onset of obesity.

Glossary

BMI Body mass index

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