Abnormal perfusion to the fetus can slow fetal growth and result in intrauterine growth restriction (IUGR). IUGR, or failure to reach one’s birth potential, is one of the most common complications during pregnancy and generally results from placental insufficiency. IUGR is generally not recognized before delivery, and treatment options for IUGR are limited, with early delivery being the most common. Preeclampsia is often a contributory cause of IUGR, and numerous studies indicate that individuals exposed to a preeclamptic pregnancy exhibit a higher body mass index and blood pressure during childhood and adult life. Individuals born with IUGR also demonstrate an increase in blood pressure later in life. This association forms the basis for the developmental origins of health and disease and indicates that adverse influences during fetal life that slow fetal growth program an individual for greater cardiovascular risk in later life.

Experimental models of placental insufficiency provide proof of principle that IUGR induced by reduced uterine perfusion programs an increase in blood pressure and cardiovascular risk in later life. However, in this issue of Circulation, Gaillard et al provide a direct link between reduced uterine perfusion and IUGR with increased cardiovascular risk. Using a large, prospective, longitudinal cohort, Gaillard and colleagues report that an increase in third-trimester fetoplacental vascular resistance indicative of reduced perfusion was associated with a decrease in size at birth and a later increase in total fat mass and systolic blood pressure at 6 years of age. Thus, this study indicates that assessment of fetal growth characteristics via Doppler flow velocity waveforms in the umbilical artery not only may be indicative of IUGR but also may identify an individual at greater risk for cardiovascular disease in later life.

IUGR in this study occurred in a relatively low-risk population of age-appropriate mothers who were in good health, of European descent, and from a middle-class to an upper-middle-class socioeconomic background. The socioeconomic background and health of the mother suggest that the mothers in this cohort had adequate access to proper nutrition. IUGR in this cohort was associated with higher umbilical artery vascular resistance. Thus, these findings suggest that the causative factors contributing to IUGR in this cohort were most likely not due to maternal undernutrition per se but rather improper remodeling of the uteroplacental circulation. The original hypothesis for the developmental origins of health and disease was based on a geographical association correlating high rates of infant mortality with high rates of death caused by coronary heart disease. However, the original observation noted by Barker and Osmond was from an area of depressed socioeconomic status, leading them to hypothesize that fetal undernutrition caused by poor living conditions was a causative factor in the fetal programming of cardiovascular risk. Since that original observation and formulation of what is now referred to as the developmental origins of health and disease, numerous population-based studies have noted an inverse relationship between birth weight as a crude marker of slow fetal growth and blood pressure as an indicator of increased cardiovascular risk that is present regardless of socioeconomic status. Therefore, significant evidence exists that poor nutrition to the fetus regardless of the reason, poverty or placental insufficiency, contributes to the developmental origins of chronic disease. Notably, this study by Galliard et al clearly demonstrates that the origins of increased programmed cardiovascular risk that arises from IUGR may require more than adequate nutrition to reverse the slow fetal growth that originates from improper remodeling of the maternal/uteroplacental vasculature.

Currently, it is not possible to reverse IUGR that results from uteroplacental insufficiency. Pregnancies complicated by IUGR are associated with an increased risk of perinatal morbidity and mortality, with early delivery considered the main treatment option. Infants delivered preterm often have serious, long-term health problems, including respiratory distress, problems with vision and hearing, cerebral palsy, developmental delays, and infection. In addition, individuals born preterm also exhibit a moderate increase in blood pressure in later life. Thus, not only is early delivery to prevent the immediate demise of the IUGR fetus associated with the early morbidities that accompany preterm birth, but also individuals born preterm may have an increased risk for the development of hypertension and cardiovascular disease in later life.

There are multiple causes of IUGR, yet most are thought to result from the improper modification of the spiral arteries and resulting increased placental resistance. Ultrasound technologies are advancing in their ability to detect resistance within the uterine and umbilical arteries as methods to predict adverse outcomes.
for the identification of IUGR and evaluation of fetal health.\textsuperscript{1} However, use is generally not indicated for routine screening in low-risk populations.\textsuperscript{8} Although Doppler evaluation is used for the assessment and management of high-risk pregnancies, detection rates during the first and second trimester remain low.\textsuperscript{1} Thus, reliable markers that exhibit an adequate positive predictive value for early detection of IUGR are needed. Numerous serum markers of angiogenic factors, growth factors, placental proteins, and hormones have been evaluated.\textsuperscript{11} However, to date, none of these have exhibited a strong predictive accuracy.\textsuperscript{11} Additionally, treatment options for IUGR have not been effective.\textsuperscript{8}

Proper development of the uteroplacental circulation is critical for adequate transfer of oxygen and nutrients to the fetus and removal of wastes from the fetus.\textsuperscript{12} Development of the uteroplacental circulation occurs to convert high-resistance vessels to low-resistance vessels to facilitate the growing needs of the developing fetus.\textsuperscript{12} Pijnenborg et al\textsuperscript{12} propose that this conversion occurs in 2 stages. The first stage is initiated from 8 to 10 weeks of age and involves endovascular plugging of the spiral arteries, followed by shallow invasion of the spiral arteries by trophoblast cells.\textsuperscript{12} The second stage occurs from 12 to 14 weeks of age and involves deeper trophoblast invasion of the spiral arteries to complete remodeling of the uteroplacental circulation.\textsuperscript{12} Therefore, on the basis of the direct link between reduced uterine perfusion and later cardiovascular risk reported by Galliard et al, early detection of pregnancies destined to be complicated by IUGR and the development of viable options to prevent impaired uteroplacental perfusion and subsequent IUGR are crucial not only for the health of the fetus and infant but also for the cardiovascular health of the IUGR individual throughout life.

An additional finding of merit in this study by Galliard et al involves the reported sex difference in the association between higher umbilical artery vascular resistance and IUGR, with increased total fat mass and blood pressure in girls at 6 years of age more affected than those in boys.\textsuperscript{5} Very few studies have examined whether sex affects programmed cardiovascular risk in children. Additionally, studies of children <11 years of age differ in their findings, reporting that the inverse association between birth weight, as a crude marker for slow fetal growth, and systolic blood pressure is stronger in boys than girls\textsuperscript{13} or is present in girls but not boys.\textsuperscript{14} Differences in methods for measuring blood pressure and whether birth records or recall were used for birth weights may contribute to these discrepancies. However, further studies clearly are needed to elucidate the impact of sex on programmed cardiovascular risk.

In summary, Gaillard et al\textsuperscript{6} provide a definitive link between impaired placental perfusion and slow fetal growth with programmed cardiovascular risk. Their study also indicates that sex affects cardiovascular outcome at 6 years of age after IUGR during fetal life.\textsuperscript{6} Findings from this study by Galliard and colleagues in this issue of 

\textit{Circulation} clearly demonstrate a need for the development of reliable early markers that can identify pregnancies at risk before the initiation of events leading to IUGR and preventive or treatment options to avert the adverse impact of IUGR on gestational outcome and the long-term health of the individual. Furthermore, this study also provides merit for continued monitoring of this cohort to further investigate how IUGR affects cardiovascular risk with age and how changes in the hormonal milieu via transitions through puberty, middle age, and menopause affect the sex difference in programmed risk. Clearly, additional longitudinal cohort studies are needed to clarify the long-term impact of the developmental origins of cardiovascular disease across the life span.

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None.

\section*{References}

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