Fetal origins of neonatal lung disease: understanding the pathogenesis of bronchopulmonary dysplasia

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Submitted 23 September 2011; accepted in final form 23 September 2011

IN THE EARLY 1990s, Barker and colleagues (4) proposed that early events occurring before birth could produce later onset cardiovascular disease in the adult. This “fetal origins hypothesis” sparked the beginning of a new way of thinking among clinical and basic scientists. Over the years, numerous reports have added to this idea that a key to understanding complex human diseases is to consider the pathology occurring as early as the fetal stages of development (3, 15, 17, 24, 25). The fetal lung appears to be particularly vulnerable to these processes (14). Animal studies have demonstrated marked structural abnormalities and cellular dysfunction secondary to intrauterine processes such as inflammation and hypoxia-ischemia (6, 9, 27). In this issue, Rozance and colleagues (21) utilize a sheep model of hyperthermia-induced placental insufficiency to comprehensively study fetal lung changes of intrauterine growth restriction (IUGR). They provide compelling evidence that the fetal lung is markedly altered by IUGR, with a degree of structural change and cellular dysfunction so significant that IUGR could be considered an independent risk factor for the development of later bronchopulmonary dysplasia (BPD). These and related findings in other animal models, combined with what has been reported in clinical observations, provide compelling evidence for the fetal origins of BPD (5, 16, 18–20).

IUGR is a major complication in both full-term and preterm births and a leading cause of perinatal morbidity and mortality. The incidence of IUGR is about 5% of all U.S. births and ranges from 5–12% among preterm births, depending in part on the stringency of definition of growth restriction (12, 26). The known consequences of IUGR include early and late neonatal death, as well as growth abnormalities, cardiopulmonary disease, and neurodevelopmental disabilities in survivors. A large majority of infants born with IUGR survive to neonatal intensive care unit discharge and seemingly do well. However, a growing body of evidence, inspired in part by Barker’s hypothesis, now indicates that these infants are at subsequent risk for adult cardiovascular disease, asthma, diabetes, and metabolic syndromes. Fetal programming occurs during a vulnerable period in which adverse environmental factors disrupt cell proliferation and differentiation and alter patterns of epigenetic remodeling (23). The impact of IUGR on preterm infants is even less well understood compared with term infants because these intrauterine processes are invariably disrupted by early delivery, leaving even fewer infants available for longitudinal study.

BPD is a complex, multifactorial disease of premature infants and is the most common chronic lung disease of infancy. Both intrauterine and extraterine factors have been implicated in its pathogenesis. Because the strongest predictor of BPD is an infant’s gestational age at birth, the most widely accepted understanding of BPD pathogenesis is that prolonged neonatal or extraterine exposures (e.g., hyperoxia, mechanical ventilation, and inflammation) to very immature lungs leads to chronic lung injury. However, we now understand that BPD may occur even after little or no exposure to these therapies. Despite considerable advances in management of respiratory failure in preterm infants, a new BPD has emerged that is characterized by disrupted alveolar development and pulmonary vascular remodeling (13), findings that are similar to what is reported in Rozance’s sheep model of IUGR (21). First described in the late 1990s, the pathophysiology of the “new BPD” emphasized the impact of intrauterine inflammation on the developing lung, which “primes” the lung for further insult by a host of postnatal exposures (2, 13). Whether intrauterine inflammatory processes are independent of postnatal exposures remains unclear, but it seems more likely that they are interrelated.

The role of chronic placental insufficiency as a contributor to BPD pathogenesis is a relatively understudied pathway that is only now gaining recognition (5). It is likely that some degree of placental insufficiency accompanies intrauterine inflammation, and vice versa (7). However, in animal models of endotoxin-induced intrauterine inflammation, we would note that the fetal lung changes are quite distinct from Rozance’s IUGR model (21), in that they are characterized by a diffuse infiltration of inflammatory cells and expression of various proinflammatory cytokines. Furthermore, recent clinical data indicate that fetal growth restriction, without evidence of placental or fetal infection or inflammation, is highly predictive of BPD, even after adjustment for many prenatal and neonatal characteristics (5). Rozance’s findings (21) in the IUGR model provide an important pathophysiological foundation for this emerging clinical understanding.

The findings of decreased pulmonary density and pulmonary artery endothelial cell (PAEC) dysfunction described by Rozance and colleagues (21) perhaps best represent the subgroup of BPD that is complicated by persistently elevated pulmonary arterial pressures and right-heart dysfunction. Pulmonary hypertension (PHTN) in the preterm infant with BPD is an increasingly recognized problem, affecting roughly one-third of infants with moderate-severe BPD (1, 22). PHTN associated with BPD is also associated with greater morbidity and mortality, including more severe BPD, long-term mechanical ventilation support, poor growth and neurodevelopmental outcome, and death attributable to right-heart dysfunction and multi-organ failure (10). There is an increasing awareness that this association occurs frequently in high-risk populations. For instance, in a recent epidemiological study, Slaughter and colleagues (22) reported a 37% incidence of PHTN at 1 mo of life among chronically ventilated infants with BPD. An et al.
(1) evaluated 116 infants with very low birth weight with mild to severe BPD and found a 25% prevalence of PHTN by echocardiogram. The prevalence of persistent PHTN among infants with BPD provides supportive evidence that the pulmonary vascular changes and PAEC dysfunction found in the placental insufficiency-IUGR model may be persistent and irreversible.

Despite the growing number of infants diagnosed with BPD-associated PHTN in recent years, little continues to be known about specific risk factors. IUGR is perhaps the most biologically plausible intrauterine mechanism. Premature infants who suffer from IUGR are more than twice as likely to develop BPD than their appropriate-for-gestational-age counterparts (5, 16). These clinical observations suggest that impaired somatic growth may alter the fetal lung in a manner that is specific to PHTN and underlying BPD. Recent animal studies have shown that chronic intrauterine stress alters the pulmonary circulation and disrupts critical signaling pathways responsible for promoting normal vascular growth and structure (11). Furthermore, in a hypoxic fetal environment, intrauterine stress also downregulates VEGF and endothelial nitric oxide synthase, disrupts endothelial cell growth, and leads to abnormal pulmonary vascular muscle cell proliferation (8), similar to what Rozance observed (21). Conversely, selective inhibition of VEGF in fetal lambs produced many of the same structural and physiological changes in the pulmonary vasculature (11) and indicates its fundamental importance in the structural and physiological changes in the pulmonary vascular development.


