COMMENT

Is bronchopulmonary dysplasia decided before birth?

Vineet Bhandari¹ and Abhay Lodha²*Pediatric Research* (2020) 87:809–810; <https://doi.org/10.1038/s41390-020-0819-4>

Bronchopulmonary dysplasia (BPD) is a complex disorder secondary to genetic–environmental interactions.^{1–3} The complexity in the pathogenesis of this developmental disorder has contributed to the difficulty in developing specific and effective preventative and therapeutic interventions to combat the devastating disease.⁴ The impact of this most common chronic lung disease of infancy extends beyond the neonatal intensive care unit (NICU), up to adulthood, and is a significant contributor to healthcare costs.^{5,6}

Among the environmental factors contributing to the pathogenesis of BPD, the three most well established are exposure to invasive mechanical ventilation (MV), hyperoxia, and sepsis. While the first two are post-natal, sepsis (which could be localized to the lung or systemic) can be ante- or post-natal in origin. In the antenatal scenario, the focus has been on the presence of chorioamnionitis.^{7–9} Interestingly, the role of chorioamnionitis (partly due to difficulties in diagnosis) as a contributory factor to BPD remains controversial.^{7,8,10–12} Downstream of all these factors has been the presence of persistent inflammation subverting the normal process of lung development. In the current issue of *Pediatric Research*, Mir et al.¹³ highlighted the potential role of a variety of placental pathologies and the outcomes of BPD/death and neurodevelopmental impairment (NDI) at 2 years.

In their retrospective study of neonates <29 weeks gestation,¹³ the investigators categorized placental lesions into none, 1, or ≥2 and noted that as the number of placental lesions increased, the outcomes of BPD/death and NDI were significantly increased. After controlling for confounding factors, the association with the presence of moderate-severe BPD (odds ratio [OR]: 3.9; 95% confidence interval [CI]: 1.5–10; $p < 0.01$) remained significant, but did not hold for NDI (OR: 1.6; 95% CI: 0.7–3.7; $p = 0.28$).¹³ Previous investigators have evaluated different types of placental pathologies with neonatal outcomes;^{14–25} however, the current study is the first one to assess the number of placental pathologic lesions with the neonatal outcomes of mortality, BPD, and NDI.

It is imperative to be aware of some of the limitations of the current study.¹³ There are some well-known shortcomings of a retrospective study, for example, missing or misclassification of data, among others. It is also important to recognize that causality cannot be established definitively in such retrospective epidemiologic studies. This study was not powered for the primary outcome. Moderate-severe BPD was defined solely as the need for supplemental oxygen at 36 weeks post-menstrual age. As the authors have also mentioned, data on clinical severity of illness was not collected. It is difficult to establish based on the study findings that multiple placental pathologies were the only contributing factor to NDI or was secondary to BPD or a combination of multiple factors during the NICU stay. Prolonged

MV is associated with acute inflammatory changes that might affect outcomes in premature infants. Therefore, one of the confounding factors was the duration of MV and this was not adjusted in the logistic regression model. In addition, unknown variables could be further confounders, and the fact that, despite the separate categorization of the placental pathological lesions, there is an interaction between the vascular and inflammatory pathologies reflecting the severity of each or a combination of the insult/injury.

The five independent significant placental pathologies assessed included acute histologic chorioamnionitis (AHC), high-grade villitis, maternal vascular underperfusion (MVU), fetal thrombotic vasculopathy (FTV), and small or large for gestational age (S/LGA) placentas. Among those with multiple significant placental lesions, the most common combinations were S/LGA or MVU with AHC. Interestingly, no single pathologic lesion was associated with BPD.¹³

As mentioned above, while the association of BPD with the presence of chorioamnionitis remains controversial,^{7,8,10–12} some of the other placental lesions appear to be associated with specific outcomes. For example, two studies have reported MVU/decreased villous vascularity in preterm infants who develop BPD-associated pulmonary hypertension (PH).^{16,26} A recent study reported that decreased levels of cord blood angiogenic factors (placental growth factor, granulocyte-colony-stimulating factor, and vascular endothelial growth factor A) were associated with placental MVU and BPD-PH.²⁷ Antenatal placental vasculopathy predisposing to disordered blood vessels in infants going on to develop BPD-PH might also be suggested with the association of maternal diabetes with BPD-PH, both for early and late PH, as recently reported.²⁸ It is certainly exciting to investigate the possibility of antenatal placental vasculopathy as a continuum towards a predisposition for developing early and/or late PH in infants with BPD.²⁹ Single-nucleotide polymorphisms of arginase-1 (*ARG1* rs2781666), and/or dimethylarginine dimethylaminohydrolase-1 (*DDAH1* rs480414), were associated with a decreased risk of developing of BPD-PH.^{30,31}

Thus, to answer the question posed in the title, probably not, but the antenatal origins of the possibility of BPD-PH warrants active investigation. Concerted efforts to understand the pathogenesis of BPD-PH will certainly pave dividends for an earlier identification and improved therapeutic options for a condition that has such a high morbidity and mortality. The association between BPD and the presence of various placental pathologies such as MVU, FTV, chronic villitis, villous edema, and acute chorioamnionitis has been inconsistent and has not been studied prospectively in a well-powered study. Such studies could allow physicians in NICUs to utilize the findings of placental histopathology to help counsel parents about the possibility of

¹Department of Pediatrics, Division of Neonatology, The Children's Regional Hospital at Cooper, Cooper Medical School at Rowan University, Camden, NJ, USA and ²Section of Neonatology, Department of Pediatrics, University of Calgary, Alberta Children's Hospital Research Institute, University of Calgary, Calgary, AB, Canada
Correspondence: Vineet Bhandari (bhandari-vineet@cooperhealth.edu)

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early prediction of BPD and possibly, its association for NDI, if found to be true.

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V.B. wrote the first draft. A.L. edited the manuscript and provided additional intellectual content. Both authors approved the final draft of the manuscript.

ADDITIONAL INFORMATION

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