Predicting Autism Spectrum Disorder in Very Preterm Infants

Janet S. Soul, MDCM, Sarah J. Spence, MD, PhD

Children born preterm are known to be at higher risk for developing autism spectrum disorder (ASD) compared with their term-born counterparts, with an estimated 7% prevalence of ASD based on a recent large prospective study and a meta-analysis.1,2 This high prevalence is in contrast to the currently estimated prevalence of ASD in the United States of 1.8% in the general population.3 ASD has been shown to be associated with a variety of prenatal, perinatal, and neonatal risk factors, including a variety of maternal health risk factors and medications and neonatal risk factors such as seizures, birth asphyxia, and low birth weight.4

Previously identified perinatal risk factors for ASD specific to preterm infants include factors such as low birth gestational age and birth weight, intracranial hemorrhage, and acute and chronic lung disease (CLD).5

The article by Chen et al6 in this issue of Pediatrics provides the first prospectively obtained data regarding whether there is an early developmental trajectory of prematurely born children that predicts who will develop ASD. The authors tested 319 preterm children prospectively with Bayley Scales of Infant Development examinations at 6, 12, and 24 months and used group-based trajectory modeling to assess whether early-life developmental trajectory predicted autism at 5 years of age. The approach of looking at developmental trajectory has been used in other high-risk populations, such as infant siblings of children with ASD7 or those with a specific genetic disorder (tuberous sclerosis complex) with a high prevalence of ASD.8

The authors provide the first data revealing that although a small percentage of preterm infants who develop ASD have a similar early-life trajectory to that of term-born children, with decline in mental development from age 12 to 24 months,9,10 the highest-risk group was identified as having low cognitive scores at 6 months, with further decline over time, allowing for early identification and intervention. The converse finding that infants with low cognitive scores who improve to ＞85 and those with stably high cognitive scores are at lower risk of developing ASD enables the clinician to provide reassurance to families.

Their analysis also illuminates risk factors for ASD related to preterm birth by comparing the 29 children who developed ASD with the 290 children without ASD. Notably, their study identified both nonmodifiable (eg, male sex, gestational age, and birth weight) and potentially modifiable risk factors (eg, CLD and duration of oxygen therapy) for the development of ASD. As the authors discussed, CLD is known to be a risk factor for developmental delay and cognitive impairment and/or disability, but it is unclear the extent to which the risk associated with CLD is related to brain injury and altered brain development.

One acknowledged limitation of the study was the lack of neuroimaging data, so it is unknown whether there was a contribution of identifiable brain injury to the development of ASD in their subjects. It is likely that at least

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some of the infants in the low
cognitive score group had easily
detected brain injury, such as large
cerebellar injury11 or cerebral injury
and/or impaired brain
development,12-14 both of which are
associated with low IQ and are
suspected to increase the risk of ASD.
Additionally, there were no data
regarding genetic risk factors for ASD,
which could contribute a “second hit”
to risk factors related to prematurity.
Numerous genes have now been
identified to be associated with ASD
and/or intellectual disability and
could have contributed to some cases
of ASD in this study. Male sex remains
a strong risk factor for ASD in both
preterm and term-born children, and
particularly in preterm children, male
sex may contribute to inherent
 genetic risks related to sex as well as
increased vulnerability to
 complications of preterm birth that
also increase the risk of ASD. The
importance of neuroimaging and
 genetic data relates in part to the
observation that preterm and term-
born children with ASD have been
shown to have important phenotypic
differences. In one study, boys with
ASD born preterm had higher rates of
seizures, attention-deficit/
 hyperactivity disorder, and sleep
apnea,15 suggesting a potentially
different neural substrate for ASD
than term-born children.
Perhaps most importantly, these
findings provide an opportunity for
initiating interventions in early life to
mitigate ASD before the diagnosis of
ASD can be definitively established.
Identification of a constellation of
prenatal and neonatal risk factors
could help clinicians target infants at
highest risk, while providing
reassurance to parents whose infants
are at low risk. Identification of high-
risk infants with low cognitive scores
at 6 months of age or those with
declining scores over time could
provide another opportunity to
intensify early intervention services
aimed at mitigating manifestations
and/or symptoms of ASD.
Importantly, identification of high-
risk infants by neonatal discharge
and/or 6 months of age could
improve research into novel therapies
to mitigate the manifestations of ASD,
such as communication and social-
emotional deficits or impairments.

**ABBREVIATIONS**
ASD: autism spectrum disorder
CLD: chronic lung disease

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