

## Review

&lt;Clinical Science: Congenital Heart Disease&gt;

# Neurodevelopmental Outcomes of Congenital Heart Disease: Impact, Risk Factors, and Pathophysiology

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In children with congenital heart disease (CHD), the chance of survival exceeds 80%. In this review, the impact of the neurodevelopmental challenges, risk factors, pathophysiology, and future directions of the condition is discussed. The overall outcomes of CHD are favorable. In particular, the rates of major disabilities, such as intellectual disability, sensory loss, and cerebral palsy were low. However, a characteristic pattern of feeding problems, mild motor and cognitive delays, executive dysfunction, impaired social interaction and communication skills, and behavior problems was observed to be common and may impact academic performance, employability, lifelong earnings, and quality of life. The risk factors for poor outcome include type of CHD; presence of genetic conditions; fetal and neonatal neuroimaging abnormalities; pre-, peri-, and postoperative factors associated with hypoxia and hemodynamic instability; prematurity; male sex; and family socioeconomic status and resilience. In utero, CHD may affect cerebral blood flow and oxygenation with resultant slower brain growth, delayed brain maturation, and white matter vulnerability. Pre- and peri-operative instability may cause brain injury, such as white matter injury, microhemorrhages, and stroke. Operative factors, such as deep hypothermic cardiac arrest and cardiopulmonary bypass, played a minor role in determining long-term outcomes. Postoperatively, prolonged hospital stay and severity of illness were predictors of worse outcome. Provision of a nurturing environment with good growth, loving touch, and supportive parents was less studied but probably very important. Future directions should focus on neurodevelopmental screening and surveillance according to existing guidelines; these include early intervention and neurorehabilitation of problems identified, neuromonitoring in the perioperative period to optimize cerebral blood flow and oxygenation, audit and quality improvement, and family education and support.

Keywords: congenital heart disease, neurodevelopmental disorders, MRI, executive function, quality of life

## Introduction

Congenital heart disease (CHD) is common and affects 9 of 1000 live births.<sup>1)</sup> One third of children with CHD require surgical or catheter intervention in early life.<sup>2)</sup> In the last 30 years, survival rates have improved dramatically, with 85% surviving until adulthood.<sup>3)</sup> The number of adult survivors with CHD is now greater than that of children with CHD.<sup>1)</sup> The type of lesion is an important determinant of survival. Simple CHD, which includes atrial and ventricular septal defects and isolated valve disease, has a 95% survival rate; whereas moderate

CHD, such as coarctation of the aorta, atrioventricular septal defects, complex ventricular septal defects, and Tetralogy of Fallot (TOF), has a 90% survival rate.<sup>1)</sup> The most dramatic improvement was seen in patients with complex CHD, such as univentricular lesions, truncus arteriosus, and complex transposition of the great arteries, at a remarkable survival rate of >80%.<sup>1)</sup> With these impressive developments, the health, well-being, and quality of life (QOL) of these new survivors have become increasingly important. Parents, families, the health care system, and the society need to understand what the future holds for newborns with CHD. The future goals

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for the care of children with CHD must include identifying and preventing adverse outcomes whenever possible and, in case adverse outcomes occur, minimizing the disease impact and improving the QOL.

This review will focus on the effect of CHD on the brain and neurodevelopment, which can have a major lifelong impact on the function of individuals. The neurodevelopmental outcomes in children with CHD and the associated risk factors will be described, along with an overview of the possible mechanisms. Recommendations on the diagnosis, rehabilitation, and prevention of these conditions will be given.

### Neurodevelopmental Outcomes in Individuals with Congenital Heart Disease

In general, the majority of children born with CHD in the current era are doing remarkably well. Considering that the survival of patients with the most complex cardiac lesions was unlikely in the past, studies on the outcomes of these children were of particular interest. Intelligence and motor development were in the low-normal range, on average. Nonetheless, a pattern of evolving neurodevelopmental and behavioral challenges throughout childhood was observed to be common and significantly affected the lives of these children and their families, especially those with complex cardiac lesions. The presence of a genetic or chromosomal condition negatively affected the prognosis and will be discussed separately below.

A child with CHD is on a different life trajectory than healthy term born children. Parents of children with CHD are typically given the diagnosis early in their child's life and then the reality of additional medical care and interventions, such as surgical or catheter treatment. These health events may lead to a much different life experience for the child, parents, and family compared to a healthy baby. Weight gain and feeding may be more difficult<sup>4,9)</sup> and the presence of hypotonia, poor oral-motor coordination, and abnormal suck-swallow coordination could pose additional feeding challenges in these babies. Infants with single-ventricle physiology have been described as being more difficult to soothe than infants with biventricular cardiac lesions<sup>10)</sup>; this situation is an additional hurdle for caregivers.

The typical pattern starts in infancy, with abnormalities in muscle tone, poor suck and swallow, feeding difficulties, and delayed developmental milestones. In early

childhood, difficulties with language, mostly articulation and expression, and social skills may become apparent. At school age, unexpected behavioral problems, including autism and attention deficit disorder; learning difficulties; and poor academic performance can emerge. Adult survivors with CHD may have increased exercise intolerance, poor weight gain or obesity, medication burden, and mental health struggles.<sup>4)</sup> For each individual, the number and severity of these deficits encompass a spectrum and are affected by risk and resilience factors.

Development in infants and toddlers was often measured by the Bayley Scales of Infant Development second edition<sup>5)</sup> (BSID-II), which comprise the psychomotor development index (PDI) and the mental development index (MDI). The most current edition is the Bayley Scales of Infant and Toddler Development third edition<sup>6)</sup> (Bayley-III), which includes motor, cognitive, and language composite scores. Test scores are standardized to a mean of 100 and a standard deviation (SD) of 15. In children with CHD, the mean scores were  $93 \pm 13$  for the MDI and  $82 \pm 16$  for the PDI.<sup>4)</sup> In a cohort of 72 infants with complex CHD, 47% of which had a single-ventricle physiology, the mean values for PDI and MDI were 81 and 92, respectively, at six months of age and 80 and 94, respectively, at 12 months.<sup>7)</sup> Using the Bayley-III for assessment of 130 children who had surgery for CHD at less than two months of age showed mean composite scores of 93.4 for cognitive, 93.6 for language, and 96.8 for motor; 9% scored  $<70$  in any one of the domains.<sup>8)</sup> In the first two years of life, 42% of children with complex CHD scored below 1.5 SD on motor skills.<sup>4)</sup>

Delays in speech and language have been shown as early as the first year of life. In preschoolers, the typical delays were in articulation, expressive language, core communication, and pragmatic language with intact receptive language. Social cognition may also be adversely affected.<sup>11)</sup> Hearing impairment needs to be considered whenever there is a speech delay. Children with CHD are often exposed to ototoxic medications, such as loop diuretics and aminoglycosides. In addition, the rates of hearing loss were higher in children treated with extracorporeal life support.<sup>4)</sup>

At the age of 4 to 5 years, 165 children with complex CHD scored lower in the general adaptive and practical domains than in the conceptual and social domains of the Adaptive Behavioural Assessment System-II.<sup>12)</sup> At this age, neurodevelopmental deficits are often subtle enough

to be missed without formal standardized testing.<sup>13)</sup>

Executive function is a measure of the higher order neurocognitive processes required for goal-directed behavior and includes inhibition, working memory, planning, fluency, and ability to shift tasks. Deficits in executive function, working memory, and organizational skills are particularly common in children with CHD and contribute to lower academic performance. In addition, deficits in visual spatial skills; visual motor integration; math, language, and social skills and persistent delays in gross and fine motor skills have often been documented in school-age children with CHD.<sup>4, 11, 14)</sup> Compared with controls, 91 school-age children with CHD demonstrated significantly more frequent executive dysfunction (OR 4.37;  $p < 0.0001$ ), especially in working memory (OR 8.22) and flexibility (OR 8.05), and most were not receiving any school services.<sup>15)</sup> In adults with CHD, neurocognitive functioning revealed poor visual spatial skills and worse working memory; this poor executive function was associated with unemployment.<sup>16)</sup> In a comparison between 112 children with univentricular CHD treated with the Fontan procedure and 253 children with CHD who underwent a biventricular repair, the single-ventricle group was shown to perform less on processing speed, inattention, and impulsivity.<sup>17)</sup>

In Arkansas, an American state, children who had surgery for CHD in the first year of life, excluding those with genetic and neurologic conditions, were significantly more likely to have low proficiency scores in literacy and mathematics on grade 3 and/or 4 state exams and were more than twice as likely to need special education, compared with children without CHD (26.9% vs. 11.6%).<sup>18)</sup> The indications for receiving special education were learning disability in 6.0%, intellectual disability in 5.4%, speech and language disability in 3.9%, multiple disabilities in 2.7%, and other in 8.4%.<sup>18)</sup> In a cohort of children  $> 10$  years of age with hypoplastic left heart syndrome, 72% had decreased exercise tolerance, 41% had educational concerns, 12% had autism or attention deficit hyperactivity disorder, and 67% were frequently referred to specialists.<sup>19)</sup> Data from the National Health Interview Survey on 420 children with CHD who were compared with 180,048 children without CHD showed that the former were thrice as likely to miss more than 10 days of school in a year, had a 4.6 times higher incidence of autism and 9.1 times higher intellectual disability and

increased use of health resources.<sup>20)</sup>

QOL is an individualized measure of a person's ability to function and derive pleasure in the context of family, school, and peer relationships; it captures three domains that include physical health and functioning, psychological status, and social functioning. Although complex to measure, QOL can be elicited from children as young as 7 years. Importantly, patients often rate their own QOL higher than that of proxies, such as parents and clinicians. One study showed that CHD had a negative impact on social and educational functioning and correlated most importantly with disease severity, followed by increased health care utilization, lower self-perception and competency, and behavioral and emotional problems.<sup>11)</sup>

The impact of a diagnosis of CHD on the lives of the child, parents, caregivers, and families is not surprising. Assessment by the Parental Functional Status-II of 100 parents of children with CHD with median age of 32 months showed that 18% scored below one SD. A low functional status was correlated with financial stressors, severity of the child's CHD, and lower child functioning.<sup>21)</sup> Behavioral and emotional issues, including post-traumatic stress disorder, anxiety, and depression can occur in the child and in the family.<sup>11)</sup>

## Neurodevelopmental Outcomes and Risk Classification

The prevalence of developmental delay is strongly influenced by the type of the congenital cardiac lesion and the presence of a genetic condition. Children with mild CHD, such as isolated atrial and septal defects, have impairment rates that minimally differ from that in healthy children.<sup>4)</sup> A study of 46 children assessed at 9 years of age did show subtle cognitive deficits in visual spatial processing; deficits in language, attention, and social skills; and lower school competence rating compared with controls.<sup>22)</sup> Almost three fourths of children with moderately severe CHD (e.g., two ventricles with coarctation of the aorta, atrioventricular septal defect, complex ventricular septal defects, TOF, total anomalous pulmonary venous drainage) developed normally. Less than half of children with severe CHD and one third of those with palliated CHD were free from impairment. On the other hand, in the presence of a genetic condition, almost all children had some developmental challenges.<sup>1)</sup>

Genetic conditions were demonstrated in approximately one third of children with CHD. Chromosomal disorders included, but were not limited to, trisomy 21 and other trisomies; microdeletions, such as 22q11; and syndromes, such as CHARGE, Alagille, Noonan's and Williams.<sup>1)</sup> These genetic conditions were associated with specific neurodevelopmental disabilities even in the absence of CHD.<sup>23)</sup> For example, 22q11 deletion was associated with deficits in executive function, visual spatial skills, and attention.<sup>24)</sup> However, most longitudinal cohort studies on CHD excluded or separately accounted for children with genetic conditions.

A group of experts appointed by the American Heart Association and American Academy of Pediatrics reviewed the risk factors for adverse neurodevelopmental outcomes and developed guidelines for evaluation and management of children with CHD.<sup>1)</sup> Three categories were found to be associated with a high risk for neurodevelopmental disorder. The first category included children who underwent open heart surgery during infancy for conditions such as hypoplastic left heart syndrome, transposition of the great arteries, TOF, interrupted aortic arch, pulmonary atresia with intact ventricular septum, truncus arteriosus, and total anomalous pulmonary venous drainage. The second category included children with cyanotic CHD without cardiopulmonary bypass surgery in the first year of life (e.g., TOF with shunt placement or with pulmonary atresia and major aortopulmonary collateral arteries and Ebstein anomaly). These patients had prolonged hypoxemia, but were spared the risks associated with open heart surgery. The third category included children who had the following risk factors derived from the literature: gestational age < 37 weeks, developmental delay identified in infancy, suspected genetic abnormality or syndrome, extracorporeal life support, heart transplantation, cardiopulmonary resuscitation, postoperative hospital stay greater than two weeks, perioperative seizures related to surgery, microcephaly and significant abnormalities on neuroimaging.<sup>1)</sup>

Risk factors can also be considered from the perspective of age and surgery (i.e., in utero, preoperatively, intraoperatively, or postoperatively). The third trimester of pregnancy has emerged as a period of great interest. Abnormal cardiac anatomy in utero can alter blood flow and oxygen delivery to the developing brain and affect brain maturation and vulnerability; this will be dis-

cussed further below. Abnormalities on neuroimaging in the fetal or neonatal period are risk factors for developmental deficits and may reflect either dysmaturation or injury; in general, dysmaturation poses a greater risk. Microcephaly and an abnormal neonatal neurological exam are clinically equivalent risk factors. Particularly, in a vulnerable brain, perinatal asphyxia, cardiopulmonary arrest, or need for resuscitation might cause or exacerbate white matter or other brain injuries. In addition, low literacy scores have been shown to correlate with the 5-minute Apgar score, among other factors.<sup>18)</sup>

Balloon atrial septostomy has been shown to be a risk factor for embolic infarcts in children with transposition of the great arteries in some but not all studies. Originally, the perioperative period was studied in depth for the degree of deep hypothermic cardiac arrest, flow rate of cardiopulmonary bypass, degree of hemodilution, blood gas management, postoperative hyperthermia, systemic inflammatory response, and capillary leak because the alterations in the intraoperative hemodynamic status and cerebral perfusion are modifiable.<sup>4, 25)</sup> However, a large international cohort study demonstrated that the association between perioperative factors and neurodevelopment, as measured by the BSID-II, was weak and accounted for only 5% of the variance among patients.<sup>26)</sup> Despite changes and improvements that addressed perioperative risk factors, only a modest improvement in BSID-II scores was observed over time, even after adjustment for risk factors.<sup>27)</sup> On the other hand, almost 30% of the variance in PDI and MDI scores were explained by patient and preoperative factors, center, and year of birth.<sup>27)</sup> Duration of postoperative hospital stay<sup>18)</sup> and the need for invasive rescue interventions, such as extracorporeal life support, were risk factors for worse outcome.<sup>26)</sup> As a marker of poor perfusion, increased lactate was a risk factor for low scores on the Bayley-III.<sup>8, 28)</sup>

In addition to genetic syndromes and type of cardiac lesion, patient-specific risk factors including younger gestational age, lower birth weight, and male sex were shown to affect the neurodevelopmental outcomes of children with CHD.<sup>1, 8)</sup> Gestational age is important. A study of 14-year-old children who underwent the Fontan procedure showed that compared with children born at 39 weeks or later, children born at 37 to 38 weeks gestational age performed worse in terms of executive functioning and were more likely to have attention

deficit hyperactivity disorder and psychiatric symptoms.<sup>29)</sup> School-age boys with CHD were more likely to have executive dysfunction and poor behavioral regulation than girls.<sup>15)</sup> The other important determinants of outcome were family-related and environmental factors, such as race, overprotection, maternal mental health, and socioeconomic status.<sup>18, 25)</sup>

## Pathophysiology

Understanding the pathophysiology of adverse neurodevelopmental outcomes in children with CHD needs to start with a consideration of fetal brain abnormalities. The observations of preoperative microcephaly and abnormal neurologic findings by Majnemer and Limperopoulos provided the first clues.<sup>30)</sup>

Fetal and neonatal MRI studies have demonstrated abnormalities in brain structure and brain growth, such as decreased brain volume, delayed brain maturation with decreased myelination, and abnormal metabolism. Preoperative three-dimensional volumetric MRI of children with complex CHD showed the association of reduced subcortical grey matter with increased cerebrospinal fluid volume. In cyanotic infants, reduced subcortical grey matter volume was a marker of overall worse neurodevelopment and behavior; whereas in acyanotic infants, lower cerebellar volumes correlated with worse behavioral state regulation.<sup>31)</sup> In another study on 48 children with biventricular CHD, lower total brain volume correlated with worse communication skills at one year of age, but not with the BSID-II.<sup>32)</sup> As summarized in a systematic review of fetal MRI studies by Khalil et al.,<sup>33)</sup> structural lesions were identified in 28% of CHD cases and included ventriculomegaly, agenesis of the corpus callosum, ventricular bleeding, increased extraaxial fluid, and cerebellar hypoplasia. Decreased fetal brain volume was identified in 6 of 7 studies of fetuses of all gestational ages with CHD and in all studies with imaging in the latter half of pregnancy. The associated findings were delayed cortical folding with relatively shallow parietooccipital, cingulate, and calcarine fissures. All three studies on brain metabolism and/or brain maturity demonstrated significant abnormalities.

Using Doppler ultrasound, decreased cerebral oxygen saturation and cerebral blood flow have been observed in fetuses with various congenital cardiac lesions.<sup>33)</sup> These results supported the hypothesis that decreased cerebral blood flow, nutrient supply, and cerebral oxygen

saturation impaired the brain maturation of fetuses with complex CHD.<sup>14)</sup> The brain maturation of a term newborn with complex CHD was estimated to be delayed by one month. The diffuse white matter injury seen in term children with CHD was similar to that seen in premature infants, in whom the oligodendrocyte precursor cells, which are particularly vulnerable to hypoxia and ischemia, fail to differentiate into more mature oligodendrocytes.<sup>23)</sup> The similar neurodevelopmental cognitive and motor challenges between these two population of children with diffuse white matter injury further supported the hypothesis. Therefore, a newborn with CHD might have a smaller, less mature brain and might be more vulnerable to the CHD-associated hemodynamic instabilities and hypoxia in the perinatal and perioperative periods.

After birth, hemodynamic instability, hypoxia, ischemia, and other threats to cerebral perfusion may cause further neurologic injury. Antenatal diagnosis of CHD provides an opportunity to minimize these instabilities. As expected, compared with prenatal diagnosis TOF or single-ventricle physiology, postnatal diagnosis was associated with increased brain injury and slower development of the white and grey matter of the brain. However, infants with a prenatal diagnosis of CHD, in comparison with those postnatally diagnosed, were delivered significantly earlier (38.6 weeks vs. 38.9 weeks) and had lower birth weight (3184 g vs. 3397 g).<sup>34)</sup>

The role of poor perioperative cerebral tissue oxygenation as a determinant of worse neurodevelopmental outcome has been supported by the following findings. Cerebral tissue oxygenation can be monitored non-invasively and intraoperatively with the use of near infrared spectroscopy (NIRS). Lower postoperative cerebral tissue oxygenation levels has been shown to predict worse neurodevelopmental outcomes, even after adjusting for the other risk factors, and might be a marker for impaired cerebral metabolic autoregulation.<sup>35)</sup> In patients with complex CHD that was repaired surgically in the first month of life, the cerebral tissue oxygenation index (CTOI) measured by NIRS correlated with poor outcome (death, PDI, or MDI <70). Increased lactate and inotrope use were also predictive of poor outcome. The area under the curve was 0.75 using CTOI alone and 0.813 when CTOI and lactate were combined. The optimal cut-off was 58% for CTOI and <7.4 for lactate.<sup>28)</sup> In children who had a biventricular repair, cerebral blood

flow on Doppler ultrasound correlated with ICU length of stay and 18-hour postoperative blood flow velocity correlated with lower PDI and MDI at the age of one year and brain injury on MRI.

Several markers of early brain injury have been studied and include the S100B protein, activin A, adrenomedullin, and plasma glial fibrillary acidic protein.<sup>36, 37)</sup> The latter is an early marker of brain injury that increased during cardiopulmonary bypass and peaked at the end of rewarming in 69 children with biventricular cardiac lesions and increased with a greater degree of hypothermia.<sup>37)</sup>

Cortical brain activity can be measured by amplitude integrated EEG and correlated with the 4-year neurodevelopmental outcomes of 60 infants with CHD who underwent cardiopulmonary bypass surgery; abnormalities were seen preoperatively in 4 (6.7%) patients and postoperatively in 7 (12%) patients. Lack of return to a normal sleep-wake cycle correlated with IQ at 4 years, but not with motor outcome.<sup>38)</sup>

There might be a genetic disposition to resilience or susceptibility to brain injury. The apolipoprotein E $\epsilon$ 2 allele was revealed to be a determinant of neurologic recovery after brain ischemia in a cohort of 298 children with CHD. Compared with non-carriers, carriers of this allele scored lower by 6 points on the PDI; MDI was also lower, but this was not significant ( $p=0.058$ ).<sup>39)</sup> Stroke, presumably related to embolic events, is common both preoperatively and postoperatively and has been associated with cardiac catheterization and regional cerebral perfusion bypass strategies.<sup>14, 40)</sup> Subtle hemorrhagic lesions were seen after open heart surgery and were associated with longer bypass time and worse outcomes.<sup>23)</sup>

In immature animal models, volatile anesthetic agents lead to apoptosis and neurodegeneration. In children with hypoplastic left heart syndrome, increased exposure to volatile anesthetics was associated with lower full-scale and verbal IQ scores.<sup>41)</sup>

So far, the insults that cause brain dysmaturation or injury have been presented. It is also possible that neurodevelopment in a child with CHD is affected by a lack of positive factors, such as nutrition, skin to skin care, and home environment, which support normal childhood brain growth. However, evidence to support this hypothesis is limited. Maternal education and socioeconomic status were consistently associated with better neurodevelopment in several pediatric cohorts,

including those with CHD.<sup>12)</sup> Higher maternal education was associated with better neurodevelopmental and social emotional outcomes. In fact, there was a moderate correlation between language and social emotional competence ( $r=0.43$ ,  $p<0.001$ ).<sup>42)</sup> Growth as measured by weight, length, and head circumference z score; length of hospital stay; and need for assisted feeding correlated with MDI at 6 months of age and with PDI at 12 months of age; however, the causal pathway cannot be ascertained.<sup>7)</sup> The importance of skin to skin care and parental involvement is emerging in the preterm population<sup>43)</sup> and is worthy of further study in the CHD population.

### Detection, Rehabilitation, and Prevention

Recognition of the prevalence of the clinically significant neurodevelopmental abnormalities described above in children with CHD provides an opportunity for screening, detection, and minimizing the impact of these neurodevelopmental challenges. The American Heart Association and American Academy of Pediatrics have created a comprehensive guideline for the screening and surveillance of children with CHD, in which risk is aligned with the intensity of the investigation.<sup>1)</sup> Further work is needed to disseminate this guideline since very few primary care providers of children with CHD were familiar with these screening guidelines and only 7% of cardiologists were providing advice regarding neurodevelopmental screening.<sup>44)</sup> This guideline should be part of the core curriculum of cardiologists, as well as pediatricians.

Screening and surveillance can be provided through different models of care. An alternative screening model for children with complex CHD used an existing infrastructure from a neonatal follow-up program to create a multidisciplinary neurodevelopmental follow-up program with collaboration among the departments of cardiology, cardiothoracic surgery, pediatric and neonatal intensive care unit and the NICU Follow-Up. Of CHD patients seen, 23.4% presented with a genetic syndrome; 21.7% had neuroimaging abnormalities (12.8% severe), 26.7% received first-time referrals to early intervention services, and 13.8% were referred to new services.<sup>45)</sup>

The goals of screening and surveillance are early identification and treatment. Although neurorehabilitation is complex, advances have brought new hope and optimism for children with neurodevelopmental delays and neurologic insults. Further information on neuroreha-

bilitation can be obtained from a recent in-depth review by Maitre.<sup>46)</sup>

In the United Kingdom, recommendations for national standards have been published and are targeted at reducing post-hospital mortality and hospital readmissions. These recommendations include standards for discharge documents, as well as training and guidance on post-discharge monitoring. High risk infants, including those in the high-risk CHD category, with existing neurodevelopmental conditions, or those with length of hospital stay greater than one month were recommended to be discharged from their local hospital. A home monitoring program is recommended for infants with hypoplastic left heart syndrome, single ventricle, or pulmonary atresia. A multidisciplinary network that can perform audits and review post-discharge deaths and emergency readmissions is recommended.<sup>47)</sup>

Parents are usually the best advocates for their children and are knowledgeable of the information that they need. Parents of children with CHD identified the following as important : how to recognize and respond to a clinical deterioration; understanding the medications, tests, and labs; and understanding the prognosis and plan.<sup>48)</sup> A patient/family information page has been published and is now available.<sup>14)</sup>

The ultimate goal to improve the outcomes of children with CHD is primary prevention of brain injury and dysmaturation during the fetal period, perioperatively, and throughout childhood. To improve cerebral oxygenation in a fetus with CHD, a trial of supplemental oxygen administration to pregnant mothers has been proposed and planned.<sup>33)</sup> However, this strategy is only feasible with antenatal diagnosis of CHD. In addition, as antenatal diagnosis appears to lessen brain injury, ensuring access to skilled antenatal ultrasound diagnosis should be available to all.

Optimizing cerebral blood perfusion and oxygenation is a promising technique to monitor and reduce the likelihood of perioperative brain injury. Neuroprotective strategies in the perioperative period should be built on routine neuromonitoring with NIRS, cerebral Doppler ultrasound, or possibly, serum markers.

In the neonatal intensive care unit, there is an increasing awareness of the effects of pain, stress, and a lack of skin to skin care on the newborn, as well as the importance of parent-infant interaction and parental well-being for normal infant brain development.

Optimal support of parents and families of children with CHD must be a priority.

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