Minimizing the Risk of Preoperative Brain Injury in Neonates with Aortic Arch Obstruction

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Objective To determine whether prenatal diagnosis lowers the risk of preoperative brain injury by assessing differences in the incidence of preoperative brain injury across centers.

Study design From 2 prospective cohorts of newborns with complex congenital heart disease studied by preoperative cerebral magnetic resonance imaging, one cohort from the University Medical Center Utrecht (UMCU) and a combined cohort from the University of California San Francisco (UCSF) and University of British Columbia (UBC), patients with aortic arch obstruction were selected and their imaging and clinical course reviewed.

Results Birth characteristics were comparable between UMCU (n = 33) and UCSF/UBC (n = 54). Patients had a hypoplastic aortic arch with either coarctation/interruption or hypoplastic left heart syndrome. In subjects with prenatal diagnosis, there was a significant difference in the prevalence of white matter injury (WMI) between centers (11 of 22 [50%] at UMCU vs 4 of 30 [13%] at UCSF/UBC; $P < .01$). Prenatal diagnosis was protective for WMI at UCSF/UBC (13% prenatal diagnoses vs 50% postnatal diagnoses; $P < .01$), but not at UMCU (50% vs 46%, respectively; $P > .99$). Differences in clinical practice between prenatally diagnosed subjects at UMCU vs UCSF/UBC included older age at surgery, less time spent in the intensive care unit, greater use of diuretics, less use of total parenteral nutrition ($P < .01$), and a greater incidence of infections ($P = .01$). In patients diagnosed postnatally, the prevalence of WMI was similar in the 2 centers (46% at UMCU vs 50% at UCSF/UBC; $P > .99$). Stroke prevalence was similar in the 2 centers regardless of prenatal diagnosis (prenatal diagnosis: 4.5% at Utrecht vs 6.7% at UCSF/UBC, $P = .75$; postnatal diagnosis: 9.1% vs 13%, respectively, $P > .99$).

Conclusion Prenatal diagnosis can be protective for WMI, but this protection may be dependent on specific clinical management practices that differ across centers. *(J Pediatr 2014;165:1116-22)*.

Neonates with complex congenital heart disease are at high risk for cerebral injury. Newborns with aortic arch obstruction, particularly those with single-ventricle physiology, have some of the highest rates of injury.[1] At school age, approximately one-third of these children manifest problems, varying from motor problems to difficulties in executive function.[2,3] Preoperative cranial magnetic resonance imaging (MRI) studies have revealed evidence of injury in 28%-43% of these patients, with this percentage increasing to 34%-72% after surgery.[4-7] The majority of the lesions detected on MRI are white matter injury (WMI), and a small proportion are strokes.

Brain injuries occur as the cumulative result of both the genetic background of the patient and the altered circulation during fetal, preoperative, intraoperative, and postoperative periods.[8] Numerous different risk factors are involved, including clinical management practices, such as balloon atrial septostomy and timing of surgery.[9,10] A surprising degree of clinical practice pattern variability exists across major pediatric congenital heart surgery programs. A recent single-ventricle reconstruction trial testing the effects of different Norwood shunt types among North American centers found significant variation in rates

ADC	Apparent diffusion coefficient	TE	Echo time
CPR	Cardiopulmonary resuscitation	TGA	Transposition of the great arteries
DWI	Diffusion-weighted imaging	TR	Repetition time
HLHS	Hypoplastic left heart syndrome	UBC	University of British Columbia
ICU	Intensive care unit	UCSF	University of California San Francisco
LCOS	Low cardiac output syndrome	WMI	White matter injury
MRI	Magnetic resonance imaging		

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of common clinical practices, including prenatal diagnosis (55%-85%), preoperative intubation (29%-91%), and enteral feeding (1%-100%).[11]

Prenatal diagnosis particularly affects clinical practice, allowing for planned delivery and perinatal management in a tertiary care center. Changes in clinical care afforded by prenatal diagnosis have been postulated to influence both surgical and neurodevelopmental outcomes.[12,13] Although prenatal diagnosis did not appear to be protective for preoperative brain injury in a large group of neonates with a wide range of cardiac diagnoses,[14] this does not exclude the possibility of a beneficial effect in specific defects, such as aortic arch obstructions. In newborns with transposition of the great arteries (TGA), prenatal diagnosis was not associated with improved early neurodevelopmental outcomes.[15] At school age, however, although IQ, language, and memory was normal in children with prenatally diagnosed TGA and those with postnatally diagnosed TGA, the latter had a higher prevalence of neurocognitive deficits and worse executive function.[16]

For newborns with aortic arch obstruction, prenatal diagnosis allows for early initiation of prostaglandin E2 therapy to maintain ductal patency and results in improved preoperative clinical status.[17] The effect on brain injury remains unknown. We focused on rates of preoperative brain injury in neonates with aortic arch obstruction as related to the presence of prenatal diagnosis and clinical practice differences across centers.

Methods

Our analysis used data from 2 prospective cohorts at 3 centers performing MRI scans before and after neonatal cardiac surgery: University Medical Center Utrecht (Utrecht, The Netherlands [UMCU]), and a longstanding collaboration of the University of California San Francisco (UCSF) and the University of British Columbia (UBC; Vancouver, Canada).[1,7,18] For our analysis, UCSF and UBC were considered a single center owing to the smaller sample size of patients with arch obstruction at UBC (n = 10) and initial comparisons showing similar perioperative management at these 2 centers (**Table I**; available at www.jpeds.com). Informed consent was obtained from all participating parents and from the institutional Medical Ethical Boards.

For this study, the preoperative scans of all enrolled neonates with aortic arch obstruction were used. The 3 centers had comparable MRI protocols, resulting in a similar sensitivity for identifying abnormalities.

At UMCU, MRI was performed with a 1.5-T scanner (Philips Medical Systems, Best, The Netherlands). MRI included 2-mm-thick sagittal T1-, transverse T2-, and inversion recovery-weighted sequences. An echo-planar imaging technique was used for diffusion-weighted imaging (DWI) (repetition time [TR], 3800-5200 msec; echo time [TE], 89 msec), with a 180 × 180-mm field of view, 4-mm-thick sections, a 0-mm section gap, and b factors of 0 and 1000 s/mm^2 (1.5 T). At UCSF, a 1.5-T Signa Echo-Speed System (GE Medical Systems, Waukesha, Wisconsin) was used. Imaging included T1-weighted sagittal spin-echo images (TR, 600 msec; TE, 8 msec; field of view, 20 cm; slice thickness, 3 mm; section gap, 1 mm), dual-echo T2-weighted spin-echo images (TR, 3000 msec; TE, 60 msec; field of view, 8.3-13.5 cm; slice thickness, 4 mm; section gap, 2 mm), coronal volumetric 3-dimensional gradient echo images with radiofrequency spoiling images (TR, 36 msec; TE, 3.5 msec; field of view, 22 cm; slice thickness, 1 mm, section gap, 0), and average diffusivity map echo-planar acquisition (TR, 8000 msec; TE, 150 msec; field of view, 36 3 27 cm; slice thickness, 5 mm, section gap, 0). At UBC, MRI studies were performed with a Siemens 1.5-T Avanto system (Siemens, Erlangen, Germany) using VB 13A software, and included 3-dimensional coronal volumetric T1-weighted images (TR, 36 msec; TE, 9.2 msec; field of view, 200 mm; slice thickness, 1 mm; section gap, 0) and axial fast spin-echo T2-weighted images (TR, 4610 msec; TE, 107 msec; field of view, 160 mm; slice thickness, 4 mm; section gap, 0.2 mm). Average diffusivity maps were generated from diffusion tensor imaging acquired with a multirepetition, single-shot echo planar sequence with 12 gradient directions (TR, 4900 msec; TE, 104 msec; field of view, 160 mm; slice thickness, 3 mm, section gap, 0); b, ¼ 0, 600, and 700 s/mm^2; and an in-plane resolution of 1.3 mm.

All scans were assessed for evidence of stroke and WMI by a single reviewer (K.P.), using conventional T1-weighted imaging, T2-weighted imaging, and DWI. WMI was scored as defined previously[19] and as depicted in the **Figure** (available at www.jpeds.com). Mild WMI was defined as no more than 3 lesions each no larger than 2 mm; moderate, as 3 or more lesions or areas larger than 2 mm; and severe, as involvement of approximately >5% of the hemisphere.

Clinical data were collected by retrospective chart review. Only data for the time period before preoperative MRI were analyzed, and thus events that may have occurred between the preoperative MRI and surgery were not included.

All daily physician progress notes and transfer notes were used, as were all available laboratory data. Low cardiac output syndrome (LCOS) was defined as either the use of cardiopulmonary resuscitation (CPR) or the presence of at least 3 of any of the following variables: clinical signs of LCOS, such as tachycardia, cool extremities, poor pulses, or oliguria; laboratory data showing an increased base deficit >3 mEq/L or a lactate >3 mmol/L; or an intervention such as administration of inotropes, high-dose prostaglandin, or HCO_3^-.[20] LCOS was only scored for patients with sufficient clinical records to establish the diagnosis. Infections were assessed as defined previously.[18] All clinical and imaging data were analysed separately by category of prenatal diagnosis.

Binary variables were compared between groups using the Fisher exact test. Continuous variables were compared using the Mann-Whitney U test. Given the sample size, univariate analyses were performed. All analyses were performed using SPSS version 15 (SPSS, Chicago, Illinois).