Brain Injury and Neurodevelopmental Outcome in Congenital Heart Disease: A Systematic Review

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abstract

CONTEXT: Brain injury during prenatal and preoperative postnatal life might play a major role in neurodevelopmental impairment in infants with congenital heart disease (CHD) who require corrective or palliative surgery during infancy. A systematic review of cerebral findings during this period in relation to neurodevelopmental outcome (NDO), however, is lacking.

OBJECTIVE: To assess the association between prenatal and postnatal preoperative cerebral findings and NDO in infants with CHD who require corrective or palliative surgery during infancy.

DATA SOURCES: PubMed, Embase, reference lists.

STUDY SELECTION: We conducted 3 different searches for English literature between 2000 and 2016; 1 for prenatal cerebral findings, 1 for postnatal preoperative cerebral findings, and 1 for the association between brain injury and NDO.

DATA EXTRACTION: Two reviewers independently screened sources and extracted data on cerebral findings and neurodevelopmental outcome. Quality of studies was assessed using the Newcastle-Ottawa Quality Assessment Scale.

RESULTS: Abnormal cerebral findings are common during the prenatal and postnatal preoperative periods. Prenatally, a delay of cerebral development was most common; postnatally, white matter injury, periventricular leukomalacia, and stroke were frequently observed. Abnormal Doppler measurements, brain immaturity, cerebral oxygenation, and abnormal EEG or amplitude-integrated EEG were all associated with NDO.

LIMITATIONS: Observational studies, different types of CHD with different pathophysiological effects, and different reference values.

CONCLUSIONS: Prenatal and postnatal preoperative abnormal cerebral findings might play an important role in neurodevelopmental impairment in infants with CHD. Increased awareness of the vulnerability of the young developing brain of an infant with CHD among caregivers is essential.

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Ms Mebius conceptualized and designed the study, screened databases for eligible studies, drafted the initial manuscript, and revised the manuscript after feedback from coauthors; Dr Kooi conceptualized and designed the study, screened databases for eligible studies, and critically reviewed and revised the manuscript;

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It has been well established that infants with congenital heart disease (CHD) are at risk for neurodevelopmental impairments. Reports have been published that indicate that in complex CHD, up to 50% of the infants have neurodevelopmental impairments.[1] Impairments can manifest themselves variably, involving different aspects such as (mild) impairments in cognition, fine and gross motor skills, executive functioning, visual construction and perception, attention, social interaction, and core communication skills.[1]

Threats for the young developing brain can arise at different stages during pre- and postnatal life. Research used to focus on the intraoperative and postoperative period, but we now know that brain injury in infants with CHD may already occur before cardiac surgery.[2] Furthermore, there is increasing evidence that suggests that brain injury in infants with CHD already occurs during intrauterine life.[3]

The exact mechanism responsible for brain injury in CHD is not yet fully understood. There are 2 main theories. First, the brain could primarily develop differently in infants with CHD because of intrinsic (epi)genetic factors.[4] A large part of heart and brain development occurs simultaneously in the human fetus and involves shared genetic pathways. A discrepancy in one of these pathways could lead to abnormal development of both organs and may thus cause neurodevelopmental impairments.[5] Second, the heart defect may entail changes in oxygen saturation because of intracardiac or extracardiac mixing, which could in turn lead to circulatory alterations that affect oxygen and nutrient supply to the brain and could therefore disturb normal cerebral development.[6]

Although several studies have reported on prenatal brain injury, preoperative brain injury, or neurodevelopmental outcome (NDO) in CHD, a systematic review of brain injury during both prenatal and postnatal preoperative life in relation to NDO is currently not available. The aim of this study was, therefore, to systematically review existing evidence for prenatal and postnatal preoperative brain injury in relation to NDO in infants with complex CHD.

METHODS

Search Strategy

This systematic review was performed according to the PRISMA guidelines for systematic reviews.[7] There was no registered protocol available. A systematic search was conducted in PubMed and Embase independently by 2 researchers (M.J.M. and E.M.W.K.) on July 1, 2016. Publications from January 2000 to July 2016 that contained data on prenatal and/or postnatal preoperative cerebral findings and neurodevelopmental outcome in infants with congenital heart disease were selected for this review.

To assess all available literature on prenatal and postnatal preoperative brain injury in relation to NDO, we conducted 3 different searches. We started with a search on cerebral findings in fetuses with congenital heart disease. For this search, we selected all original research articles that were written in English and contained different combinations or synonyms of congenital heart disease, fetus, Doppler, MRI, sonography, and brain. Articles that exclusively focused on head biometry were excluded. For the second search, we used combinations or synonyms of congenital heart disease, neonate, infant, Doppler, MRI, near-infrared spectroscopy, EEG, and brain. Articles were selected if they were written in English, if participants were <3 months of age at the first examination, and if at least part of the study group was diagnosed prenatally with CHD. Articles that focused on infants with chromosomal or syndromal disorders were excluded because we were interested in the effect of the congenital heart defect on NDO in infants with complex CHD. For the purpose of the current review, we were not interested in developmental problems because of chromosomal disorders. In addition, we excluded articles with an interventional study design tailored to evaluate the direct impact of an experimental intervention on cerebral outcome variables. For the third search, we combined the first 2 searches and complemented it with neurodevelopmental outcome and word variants. Articles were selected only if they combined prenatal and/or postnatal preoperative cerebral findings with NDO in infants with CHD. Furthermore, NDO had to be assessed with validated tools such as the Bayley Scales of Infant Development II (BSID II) or the Bayley Scales of Infant and Toddler Development III (Bayley III). The complete search string is available online in Supplemental Information.

In addition to the database search, we screened the reference lists of all retrieved articles for additional relevant publications.

Quality Assessment

We assessed the quality of the selected articles using the Newcastle-Ottawa Quality Assessment Scale for case-control studies and cohort studies. This scale consists of 3 parts: selection, comparability, and exposure for case-control studies and selection,

comparability, and outcome for cohort studies. Each part consists of a different number of items and a different amount of points that can be acquired per item. Selection consists of 4 items with a maximum of 4 points, comparability consists of 1 item with a maximum of 2 points, and exposure or outcome consists of 3 items with a maximum of 3 points. Therefore, the total score ranges from 0 to 9, with 9 being an article of the highest quality. The quality scores of selected articles are presented online in Supplemental Tables 4 and 5.

RESULTS

Our initial search resulted in 503 articles. After removing duplicates, we assessed titles and abstracts of 260 articles, of which 40 were relevant. The main reasons for exclusion were chromosomal or syndromal disorders, not original research, and study being out of scope. From the reference lists, we found 7 additional articles. After reading the full text, 30 articles were included in the prenatal part of the review (Fig 1). Prenatal cerebral findings are presented in Table 1.

The second search resulted in 1347 articles. We assessed titles and abstract of 734 articles after removing duplicates. Reasons for exclusion at this stage were chromosomal or syndromal disorders, not original research, intraoperative or postoperative data, and study being out scope. From the reference lists, we found another 3 articles. Eventually, we read 68 full-text articles, from which 51 were included in the postnatal part of the review (Fig 2). Postnatal cerebral findings are presented in Table 2.

The final search resulted in 882 articles. Many articles on neurodevelopmental outcome were not eligible because they did not combine prenatal or postnatal preoperative cerebral findings with neurodevelopmental outcome. Four additional relevant articles were found and added to either the prenatal or the postnatal preoperative part of the review. Results on the association between prenatal or postnatal preoperative cerebral findings and neurodevelopmental outcome are presented in Table 3.

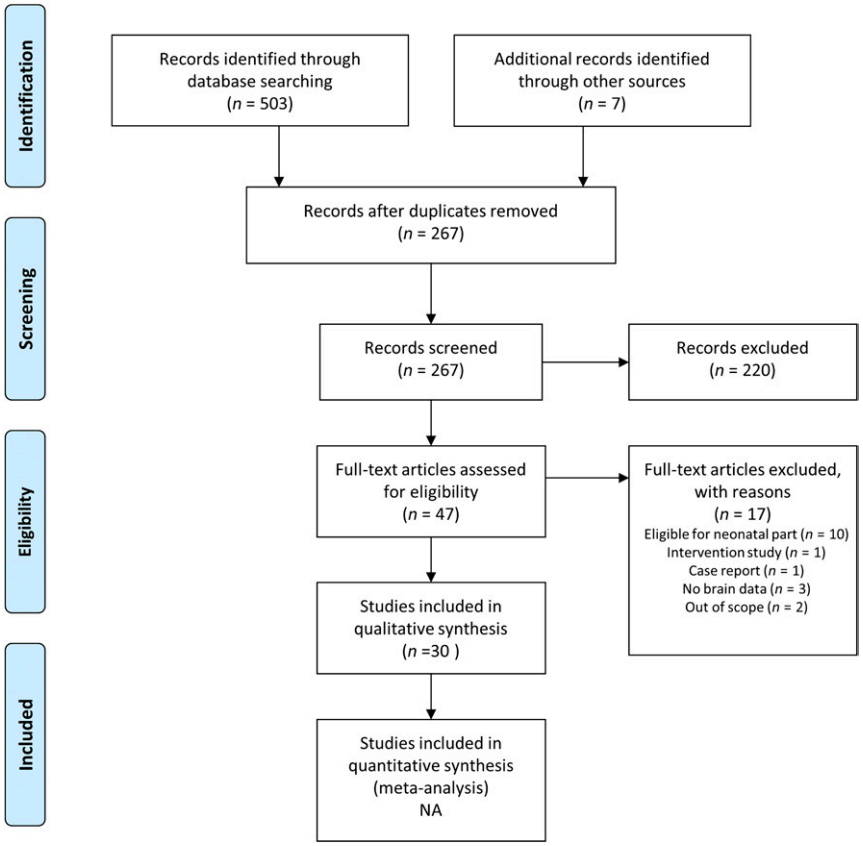

FIGURE 1
Prenatal search strategy. NA, not applicable.

Prenatally, 1 study included a small percentage of infants with nonisolated CHD, 13% of the studies did not report on whether they included infants with nonisolated CHD, and 84% focused exclusively on infants with isolated CHD. Postnatally, 32% of the studies did not report on including or excluding infants with nonisolated CHD and 1 study included a small percentage of infants with nonisolated CHD. When possible, only the results of infants with isolated CHD were presented.

Prenatal Cerebral Ultrasound

Twenty-two articles reported on Doppler parameters (Table 1). In general, these studies were case-control studies or cohort studies that compared Doppler parameters of fetuses with CHD with either healthy controls or reference values from the literature. Almost all studies used *z* scores to adjust for gestational age (the amount of SDs from the mean for a given gestational age).

The vast majority (86%) of the 22 studies that reported on Doppler parameters found the pulsatility index (PI) of the middle cerebral

TABLE 1 Prenatal Cerebral Findings in Infants with CHD

Study (First Author, Journal, Year of Publication)	Study Design, No. Infants	CHD	Age	Methods	Findings (Compared With Healthy Controls and/or Reference Values, Unless Otherwise Stated)[a]
Ruiz et al, Ultrasound *Obstet Gynecol*, 2016	Retrospective study, *N* = 119	Mixed	Second and third trimester	Ultrasound (biometry, Doppler)	Normal MCA-PI and CPR during second trimester; 18% MCA-PI and CPR less than fifth percentile at first examination Lower MCA-PI in group with severe impairment of cerebral blood flow UA-PI increased with GA Smaller HC and BPD at diagnosis which remained during pregnancy
Hahn et al[b], *Ultrasound Obstet Gynecol*, 2016	Retrospective study, *N* = 133	SVA	Second and third trimester	Ultrasound (biometry, Doppler)	Lower MCA-PI and decreased more as GA progressed Smaller HC at 24–29 wk GA and >34 wk GA Fetal HC predictor of neonatal HC from 30 wk GA MCA-PI not associated with fetal and neonatal HC
Zeng et al, *Ultrasound Obstet Gynecol*, 2015	Case-control study, *N* = 73/168	Mixed	Second and third trimester	Ultrasound (biometry, Doppler)	Lower MCA-PI Total intracranial volume, frontal lobe volume, cerebellar volume, and thalamus volume progressively decreased from 28 wk GA Largest decrease in frontal lobe volume, followed by total intracranial volume and cerebellar volume Smaller HC and BPD from 33 wk GA
Zeng et al[b], *Ultrasound Obstet Gynecol*, 2015	Case-control study, *N* = 112/112	Mixed	20–30 wk	Ultrasound (Doppler)	Lower MCA-PI in HLHS, MCA-PI tended to be lower in LSOL, normal MCA-PI in TGA and RSOL Higher cerebral blood flow Vascularization index, flow index, and vascularization flow index of the total intracranial volume and 3 main arteries higher in HLHS and LSOL and of the anterior cerebral artery in TGA
Masoller et al, *Ultrasound Obstet Gynecol*, 2014	Case-control study, *N* = 95/95	Mixed	20–24 wk	Ultrasound (biometry, Doppler)	Lower MCA-PI and CPR and higher fractional moving blood volume Fractional moving blood volume >95th percentile in 81% compared with 11% in controls No differences in MCA-PI and fractional moving blood volume between CHD diagnostic groups Smaller BPD and HC No differences in BPD and HC between CHD diagnostic groups
Williams et al[b], *Am Heart J*, 2013	Cohort study, *N* = 134	SVA	18–38 wk	Ultrasound (Doppler)	MCA-PI at first fetal echocardiogram −0.95 ± 1.5 22% MCA-PI < −2.0 at least once across gestation
Yamamoto et al, *Ultrasound Obstet Gynecol*, 2013	Case-control study, *N* = 89/89	Mixed	32 wk	Ultrasound (biometry, Doppler)	Lower MCA-PI, higher UA-PI and lower CPR in HLHS and CoA CoA with retrograde aortic arch flow, lower MCA-PI and CPR, and higher UA-PI compared with CoA with antegrade flow Normal MCA-PI, UA-PI, and CPR in TGA and POTO Smaller HC at birth in TGA and CoA
Szwast et al, *Ultrasound Obstet Gynecol*, 2012	Retrospective study, *N* = 131/92	SVA	18–40 wk	Ultrasound (Doppler)	Lower MCA-PI and lower CPR in aortic arch obstruction compared with controls and compared with pulmonary obstruction MCA-PI decreased during gestation for aortic obstruction MCA-PI increased during gestation for pulmonary obstruction Normal UA-PI
Williams et al[b,c], *Ultrasound Obstet Gynecol*, 2012	Pilot study, *N* = 13	Mixed	20–24 wk	Ultrasound (Doppler)	MCA-PI −1.7 ± 1.1 56% CPR < 1.0 (no *z* scores) HLHS and TOF lowest MCA-PI (−2.4 and −2.01, respectively), TGA −0.75
Arduini et al, *J Matern Fetal Neonatal Med*, 2011	Case-control study, *N* = 60/65	Mixed	30–38 wk	Ultrasound (biometry, Doppler)	Lower MCA-PI and CPR (no *z* scores) HLHS and CoA lowest and TOF and TGA highest CPR Smaller HC and HC/AC HLHS and CoA lowest and TOF and TGA highest HC/AC
Itsukaichi et al, *Fetal Diagn Ther*, 2011[8]	Retrospective study, *N* = 44/140	Mixed	28–34 wk	Ultrasound (biometry, Doppler)	MCA-RI measurements more often less than fifth percentile and UA-RI >90th percentile Similar biometry measurements in fetuses <10th and >10th MCA-RI percentile
McElhinney et al, *Ultrasound Med Biol*, 2010	Cohort study, *N* = 52 HLHS	HLHS	20–31 wk	Ultrasound (Doppler)	Lower MCA-PI and RI in HLHS Normal UA-PI and UA-RI 37% CPR <1.0 (no *z* scores)
Berg et al, *Ultrasound Obstet Gynecol*, 2009	Case-control study, *N* = 113/1378	Mixed	19–41 wk	Ultrasound (biometry, Doppler)	Smaller HC at birth, normal MCA-PI and CPR in TGA Smaller HC at birth, lower MCA-PI and CPR in HLHS Normal biometry and Doppler parameters in PA, AoS, and TOF

TABLE 1 Continued

Study (First Author, Journal, Year of Publication)	Study Design, No. Infants	CHD	Age	Methods	Findings (Compared With Healthy Controls and/or Reference Values, Unless Otherwise Stated)[a]
Guorong et al, *Fetal Diagn Ther*, 2009	Case-control study, *N* = 45/275	Mixed	20–40 wk	Ultrasound (Doppler)	Normal MCA-PI MCA-PI tended to be lower in LSOL and was lower in congestive heart failure Higher UA-PI and higher U/C PI ratios No traditional "brain sparing" as MCA-PI was normal, whereas U/C PI was higher
Chen et al, *Am J Perinatol*, 2009	Case-control study, *N* = 11/44	Ebstein anomaly	23–37 wk	Ultrasound (Doppler)	Lower MCA-PI and CPR (no *z* scores) Higher UA-PI and left ventricular myocardial performance index Lower fetal cardiac profile score (median 1 point lower) MCA-PI positive correlation with cardiovascular profile score and negative correlation with left ventricular myocardial performance index
Modena et al, *Am J Obstet Gynecol*, 2006	Case-control study, *N* = 71/71	Mixed	24–28 wk	Ultrasound (Doppler)	Normal MCA-PI, UA-PI, and CPR MCA-PI more often less than fifth percentile (5/71 vs 0/71) CPR more often less than fifth percentile (8/71 vs 2/71) No difference in UA-PI >95th percentile (6/71 vs 3/71)
Kaltman et al, *Ultrasound Obstet Gynecol*, 2005	Case-control study, *N* = 58/114	Mixed	20–40 wk	Ultrasound (Doppler)	Lower MCA-PI in HLHS Higher MCA-PI in RSOL compared with HLHS Higher UA-PI in RSOL U/C PI-ratio similar between diagnostic groups
Donofrio et al, *Pediatr Cardiol*, 2003	Case-control study, *N* = 36/21	Mixed	Second and third trimester	Ultrasound (Doppler)	Lower MCA-RI and CPR Normal UA-RI HLHS and HRHS infants had highest incidence of abnormally low CPR (58% and 60%)
Jouannic et al, *Ultrasound Obstet Gynecol*, 2002	Case-control study, *N* = 23/40	TGA	36–38 wk	Ultrasound (Doppler)	Lower MCA-PI Normal UA-PI, DV-PI, and Ao-PI (no *z* scores)
Meise et al, *Ultrasound Obstet Gynecol*, 2001	Case-control study, *N* = 115/100	Mixed	19–41 wk	Ultrasound (Doppler)	Normal MCA-PI Higher UA-PI No difference in UA-PI >95th percentile
Brossard-Racine et al[c], *Am J Neuroradiol*, 2016	Cohort study, *N* = 103	Mixed	Second and third trimester	MRI (structural)	16% fetal brain abnormalities (6 mild ventriculomegaly, 4 increased extra-axial spaces, 2 white matter cysts, 2 inferior vermian hypoplasia, 1 white matter signal hyperintensity) 32% neonatal brain abnormalities, 27% acquired brain injury Postnatally, a predominance of punctate white matter injury
Brossard-Racine et al, *Am J Neuroradiol*, 2014	Case-control study, *N* = 144/194	Mixed	18–39 wk	MRI (structural)	23% brain injury compared with 1.5% for controls Most common: mild unilateral ventriculomegaly and increased extra-axial CSF spaces No association between type of brain injury and CHD diagnosis
Mlczoch et al[b], *Eur J Paediatr Neurol*, 2013	Retrospective study, *N* = 53	Mixed	20–37 wk	MRI (structural)	39% brain injury (7 malformation, 5 acquired lesion, 9 asymmetry of the ventricles/wider CSF spaces) Fetuses with similar PA and Ao size had higher prevalence of brain injury compared with fetuses with PA < Ao or Ao < PA
Schellen et al, *Am J Obstet Gynecol*, 2015	Retrospective study, *N* = 24/24	TOF	25 wk	MRI, volume	Lower total brain volume and cortical and subcortical volumes from 20 wk GA Higher ventricular volumes and cerebrospinal fluid spaces Normal intracranial cavity volume and cerebellar volume
Al Nafisi et al, *J Cardiovasc Magn Reson*, 2013[9]	Case-control study, *N* = 22/12 controls	Mixed	30–39 wk	MRI, volume	6 fetuses brain weights less than fifth percentile, 0 controls brain weights <25th percentile 19% lower combined ventricular output
Sun et al, *Circulation*, 2015	Case-control study, *N* = 30/30	Mixed	36 wk	MRI (volume, O_2 saturation)	Smaller brain volume 10% lower aorta oxygen saturation with cerebral blood flow and extraction being normal. As a result, 15% reduction in cerebral oxygen delivery and 32% reduction in oxygen consumption Reduced cerebral oxygen consumption associated with a mean 13% reduction in brain volume or 1 SD reduction in estimated brain weight *z* score

TABLE 1 Continued

Study (First Author, Journal, Year of Publication)	Study Design, No. Infants	CHD	Age	Methods	Findings (Compared With Healthy Controls and/or Reference Values, Unless Otherwise Stated)[a]
Limperopoulos et al, *Circulation*, 2010	Case-control study, *N* = 55/50	Mixed	25–37 wk	MRI (volume, metabolism)	Significantly and progressively smaller total brain volume and intracranial cavity volume Lower NAA/Cho during the third trimester 7 CHD fetuses had cerebral lactate compared with 0 controls Absence of antegrade aortic flow and presence of lactate predictors of low NAA/Cho
Masoller et al, *Fetal Diagn Ther*, 2016	Case-control study, *N* = 58/58	Mixed	36–38 wk	Ultrasound (Doppler) MRI (volume, metabolism)	Lower MCA-PI and CPR and higher frontal fractional moving blood volume Lower MCA-PI and CPR in fetuses with impaired cerebral blood flow than fetuses with near-normal or mildly impaired cerebral blood flow Smaller total and intracranial brain volume, decreased cortical development, and altered metabolism Fetuses with impairment of blood flow to the cerebrum had more severe abnormalities on MRI than fetuses with near-normal/mildly impaired blood flow to the cerebrum
Masoller et al[b], *Ultrasound Obstet Gynecol*, 2016	Case-control study, *N* = 58/58	Mixed	36–38 wk	Ultrasound (Doppler) MRI (volume, metabolism)	Lower MCA-PI and CPR and higher fractional moving blood volume Smaller HC and BPD Smaller brain, intracranial, and opercular volume and decreased sulcation Increased Ino/Cho and decreased NAA/Cho and Cho/Cr ratios MCA-PI, CPR, and fetal HC at mid gestation were independent predictors of abnormal brain development
Clouchoux et al, *Cereb Cortex*, 2013	Case-control study, *N* = 18/30	HLHS	25–37 wk	Ultrasound (Doppler) MRI, volume	Smaller brain volumes, which became progressively greater after 30 wk GA, smaller gyrification index, and smaller surface area 3–4 wk sulcation delay Low CPR and absence of antegrade aortic flow associated with decreased cortical gray matter, white matter, subcortical matter, and decreased cortical surface area

AC, abdominal circumference; Ao, aorta; Ao-PI, pulsatility index of the aorta; AoS, aortic stenosis; BPD, biparietal diameter; CoA, coarctation of the aorta; CSF, cerebrospinal fluid; DV-PI, pulsatility index of the ductus venosus; GA, gestational age; HC/AC, head circumference/abdominal circumference; HRHS, hypoplastic right heart syndrome; LSOL, left-sided obstructive lesion; MCA-RI, resistance index of the middle cerebral artery; POTO, pulmonary outflow tract obstruction; RSOL, right-sided obstructive lesion; SVA, single ventricle anomaly; TOF, tetralogy of Fallot; UA-RI, resistance index of the umbilical artery; U/C PI, pulsatility index of the umbilical artery/pulsatility index of the middle cerebral artery.

[a] Doppler parameters and biometry measurements are reported as *z* scores unless otherwise stated.

[b] Articles that also address neurodevelopmental outcome.

[c] Articles that also address postnatal findings.

artery (MCA) to be lower in the entire study group (13 articles) or in selected CHD diagnoses (6 articles). In particular, fetuses with hypoplastic left heart syndrome (HLHS) or cardiac lesions that are associated with impaired cerebral oxygen supply had a lower pulsatility index of the middle cerebral artery (MCA-PI) compared with healthy controls.[13–21] Fetuses with right-sided obstructive lesions[14,15,19,20] often had a MCA-PI similar to healthy controls. Contradictory results were reported concerning MCA-PI in fetuses with transposition of the great arteries (TGA). On the one hand, TGA is one of the lesions associated with impaired cerebral oxygen supply because venous blood from the brain is redirected to the brain. This may lead to brain sparing, as suggested by the lower MCA-PI found by some studies.[13,21,22] On the other hand, 3 studies specifically looking into the MCA-PI of fetuses with TGA found values similar to healthy controls.[14,15,19]

None of the studies on Doppler parameters in fetuses with CHD reported higher MCA-PI compared with healthy controls. Abnormally low MCA-PI was present from the second trimester onwards[23] and tended to decrease more than would be expected for gestational age.[24]

Cerebroplacental ratio (CPR) was also reported to be lower in the majority of fetuses with CHD (75% of the selected articles). Again, fetuses with HLHS tended to have a lower CPR than fetuses with right-sided obstructive lesions and TGA.[15,19] Two articles that did not use *z* scores found CPR values of <1.0 in 37% to 56% of the cases.[16,18]

Concerning PI of the umbilical artery (UA), which reflects intraplacental resistance to flow, 11 articles reported contradictory results. Five studies reported a higher pulsatility index of the umbilical artery (UA-PI),[13,20,25–27] whereas another 5 studies reported similar UA-PI[18,22,28–30] in fetuses with

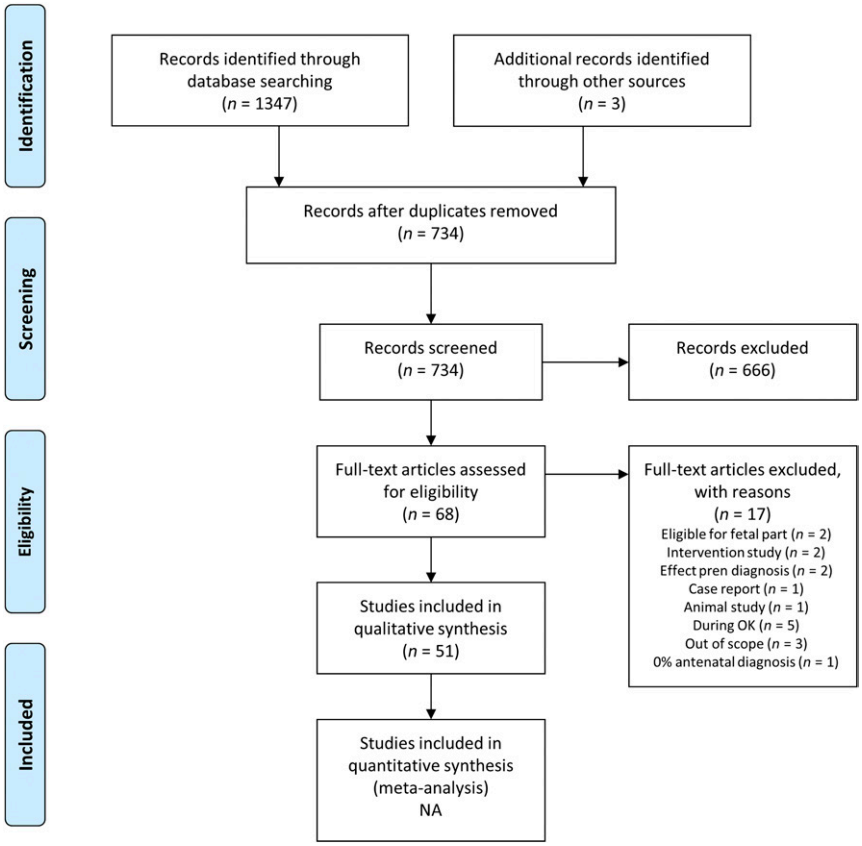

FIGURE 2
Postnatal search strategy. NA, not applicable

CHD compared with healthy controls. One study reported both higher UA-PI (coarctation of the aorta and HLHS) as well as normal UA-PI (right-sided obstructive lesions and TGA) in different parts of the study group.[15]

MRI

Prenatal MRI

The main findings on MRI in fetuses with different types of CHD (majority TGA, HLHS, tetralogy of Fallot, single ventricle anomaly) were features of developmental delay of the cerebrum. In 16% to 39% of the cases, lesions such as (unilateral) mild ventriculomegaly and increased extra-axial cerebrospinal fluid spaces were present. These abnormalities are both thought to be markers of delay of cerebral development.[31–33]

In addition to these lesions, other signs of developmental delay of the cerebrum such as a smaller head circumference (HC) and biparietal diameter, lower total brain weight, lower total brain volumes, higher ventricular volumes, and higher cerebrospinal fluid volumes were also common in fetuses with CHD.[21,33–38] Another feature of developmental delay was an impaired sulcation with a delay of ~3 to 4 weeks.[21,36–38]

Furthermore, cerebral metabolism was altered in fetuses with CHD and included an increased myo-inositol/choline (Ino/Cho), decreased n-acetylaspartate/choline (NAA/Cho), and decreased choline/creatinine (Cho/Cr) ratio.[21,33,37] These metabolic alterations are also in accordance with cerebral developmental delay.

Fetuses with CHD associated with impaired oxygen supply to the cerebrum (HLHS, critical aortic stenosis, interrupted aortic arch, and TGA) showed more pronounced developmental delay in comparison with fetuses with CHD associated with sufficient blood flow to the cerebrum.[21,34,37] Infants with HLHS showed a progressive decline in volumetric growth of the cortical and subcortical gray matter in comparison with healthy controls. These differences in brain volumes became significant from a gestational age of 30 weeks.[38] Because of the study design of most studies, a further differentiation according to the type of CHD was impossible.

Postnatal Preoperative MRI

Forty studies used MRI to examine preoperative cerebral findings in infants with different types of CHD (Table 2). Signs of delayed development of the cerebrum were also common during this period. Infants with CHD had an overall reduction of 21% in total brain volume,[39] with all brain regions being affected.[39–42] The largest regional difference between neonates with CHD and healthy controls seemed to be in the corpus callosum (31% smaller), cortical gray matter (29.5% smaller), and the occipital lobes (28.5% smaller).[39–41,43] These differences in brain volumes persisted to an age of 3 months. Brain growth rate, however, did not seem to differ between neonates with CHD and healthy controls in 1 study.[40]

Brain metabolism and microstructural development were also in accordance with delayed cerebral development. White matter fractional anisotropy[44–47] and NAA/Cho[45–47] were lower, and mean average diffusivity,[45–47] lactate/choline (Lac/Cho),[45–47] Cho/Cr,[48] and myo-inosinotol/creatinine[48] were higher. The mean total maturation scores were significantly lower than reported normative data in neonates without CHD and corresponded to a delay of ~4 weeks in structural brain development.[49] In infants with TGA, the altered metabolism was

TABLE 2 Postnatal Cerebral Findings in Infants With CHD

Study (First Author, Journal, Year of Publication)	Study Design, No. Infants	CHD	Antenatal Diagnosis	Methods	Findings (Compared With Healthy Controls and/or Reference Values, Unless Otherwise Stated)
Brossard-Racine et al, *ANJR Am J Neuroradiol*, 2016	Cohort study, *N* = 103	Mixed	100%	MRI (structural)	32% brain injury (26% acquired) WMI most common injury (5 mild and 10 moderate or severe) WMI located in the periventricular white matter, centrum semiovale, and frontal white matter Second most common injury: nonhemorrhagic parenchymal injury
McCarthy et al, *Pediatr Res*, 2015	Retrospective study, *N* = 72	Mixed	U	MRI (structural)	18% PVL The majority of PVL classified as moderate
Bertholdt et al, *Eur J Cardiothorac Surg*, 2014	Case-control study, *N* = 30/20	Mixed	17%	MRI (structural)	23% WMI or stroke, 47% intracranial hemorrhage (subdural hematoma or choroid plexus) Low Spo_2 risk factor for brain injury, BAS not associated with brain injury Brain injury associated with poorer neurologic functioning (82% abnormal assessment)
Owen et al[a], *J Pediatr*, 2014	Cohort study, *N* = 35	Mixed	51%	MRI (structural)	46% evidence of injury or immaturity on MRI (most common: hemorrhage) 71% suspect or abnormal neurobehavioral assessment (16 suspect, 9 abnormal)
Goff et al, *J Thorac Cardiovasc Surg*, 2014	Cohort study, *N* = 57	HLHS	86%	MRI (structural)	19% PVL preoperatively Brain immaturity and male sex independent strong predictors of PVL
Andropoulos et al[a], *Paediatr Anaesth*, 2014	Retrospective study, *N* = 59	Mixed	U	MRI (structural)	46% preoperative brain injury WMI most common injury (31%; 8 mild, 3 moderate, 1 severe)
Beca et al[a], *Circulation*, 2013	Cohort study, *N* = 153	Mixed	59%	MRI (structural)	26% brain injury (20% WMI, 5% stroke, 4% hemorrhage) WMI associated with brain immaturity but not with BAS, diagnostic group, or GA at birth WMI and stroke not associated with postoperative brain injury
Mulkey et al, *Pediatr Cardiol*, 2013	Retrospective study, *N* = 73	Mixed	32%	MRI (structural)	47% ≥1 type of brain injury, 26% 2–4 injury types 25% brain injury if hemorrhage was excluded Lower Apgar score at 5 min associated with brain injury
Ortinau et al, *J Pediatr*, 2013	Case-control study, *N* = 15/12	Mixed	U	MRI (structural)	Reduced cortical surface area and gyrification index for left and right hemispheres 46% focal signal abnormalities in the white matter
Glass et al, *Cardiol Young*, 2011	Cohort study, *N* = 127	Mixed	U	MRI (structural)	24% white matter injury Infants with TGA and blood stream infection might have a higher risk of developing WMI (not significant in the whole group but significant when stroke was excluded)
Block et al, *J Thorac Cardiovasc Surg*, 2010	Cohort study, *N* = 92	TGA SVA	U	MRI (structural)	43% brain injury (23 stroke, 21 WMI, and 7 IVH) BAS doubled the risk for brain injury Higher Spo_2 protective factor for brain injury (OR = 0.96)
Andropoulos et al, *J Thorac Cardiovasc Surg*, 2010	Cohort study, *N* = 67	Mixed	44%	MRI (structural)	28% brain injury (single ventricle and 2 ventricles) Brain immaturity associated with preoperative WMI and late death 58% of lesions partially or completely resolved at late MRI scan (3–6 mo)
Beca et al, *J Am Coll Cardiol*, 2009	Cohort study, *N* = 64	Mixed	32%	MRI (structural)	30% brain injury (27% WMI and 5% stroke) No differences between cardiac diagnoses No association between BAS and brain injury
Petit et al, *Circulation*, 2009	Retrospective study, *N* = 26 (14 BAS)	TGA	U	MRI (structural)	38% PVL, 0 strokes Arterial oxygen saturation and time to surgery risk factors for brain injury No association between BAS and brain injury
Licht et al, *J Thorac Cardiovasc Surg*, 2009	Cohort study, *N* = 42	TGA HLHS	83% HLHS 39% TGA	MRI (structural)	21% PVL, 9.5% stroke, 86% incomplete closure of the opercular space (brain immaturity) Lower total maturation scores (10.15), ~1 mo younger than their actual GA
McQuillen et al, *Circulation*, 2006	Cohort study, *N* = 29	TGA	U	MRI (structural)	41% brain injury (5 stroke, 2 WMI, 1 IVH, 4 combination of lesions) 5 min Apgar score, lowest Spo_2, and BAS (12 of 19 infants with BAS had brain injury, 0 of 10 without BAS had brain injury) are risk factors for brain injury
Durandy et al, *Artif Organs*, 2011	Cohort study, *N* = 21	TGA	57%	MRI (structural)	42% brain injury (4 infarct, 4 WMI, and 5 hemorrhages in 9 infants) 55% brain injury in antenatal diagnosis compared with 33% in postnatal diagnosis

TABLE 2 Continued

Study (First Author, Journal, Year of Publication)	Study Design, No. Infants	CHD	Antenatal Diagnosis	Methods	Findings (Compared With Healthy Controls and/or Reference Values, Unless Otherwise Stated)
Tavani et al, *Neuroradiology*, 2003[10]	Cohort study, *N* = 24	Mixed	U	MRI (structural)	62% of infants delivered vaginally had hemorrhage on MRI 11 subdural hematomas 6 blood in the subdural space along the tentorium and falx or more laterally 7 blood in the choroid plexus No relation between intracranial hemorrhage and abnormal neurologic examination
von Rhein et al, *J Pediatr*, 2015	Case-control study, *N* = 19/19	Mixed	U	MRI, volume	21% total brain volume reduction, all regions affected Smallest difference: mesencephalon 7.7% smaller Biggest difference: cortical gray matter 29.5% smaller and occipital lobes 28.5% smaller
Ortinau et al, *Pediatr Cardiol*, 2012	Cohort study, *N* = 57/36	Mixed	U	MRI, volume	Smaller frontal, parietal, cerebellar, and brain stem measures Brain growth rate not different Differences in volume persisted at 3 mo, except for cerebellar measures Somatic growth the greatest predictor of brain growth
Ortinau et al, *J Thorac Cardiovasc Surg*, 2012	Cohort study, *N* = 67/36	Mixed	U	MRI (structural, volume)	42% focal WMI Smaller frontal, parietal, cerebellar, and brain stem Frontal and brain stem most affected Delayed maturation at the microstructural level
Makki et al, *AJNR Am J Neuroradiol*, 2013[11]	Case-control study, *N* = 15/11	TGA	U	MRI (DTI)	Higher apparent diffusion coefficient, lower FA genu corpus callosum Lower FA splenium corpus callosum
Hagmann et al, *J Child Neurol*, 2016	Case-control study, *N* = 22/22	Mixed	U	MRI (volume, DTI)	Corpus callosum 25% (splenium) to 35% (genu) smaller Total corpus callosum and splenium significantly smaller Splenium lower FA, higher radial diffusion, diffusion coefficient not significant No differences in other substructures of the corpus callosum
Mulkey et al, *Pediatr Neurol*, 2014	Pilot study, *N* = 19	Mixed	U	MRI (structural, DTI)	52% brain injury (WMI or stroke) Lower FA in multiple major white matter tracts in infants with brain injury compared with infants without brain injury
Partridge et al, *Ann Neurol*, 2006	Cohort study, *N* = 25	Mixed	U	MRI (structural, DTI)	28% brain injury (focal or multifocal) Brain injury associated with less change in FA over time in the pyramidal tract compared with newborns with 2 normal MRI scans Infants with brain injury had the least dramatic changes with age detected by DTT Trend in FA maturation rates across the 3 injury groups: newborns with normal scans had the most rapid changes, those with postoperative injury had intermediate maturation rates, and those with preoperative injury had the least rapid changes No differences in directionally averaged diffusion coefficients
Sethi et al, *Pediatr Res*, 2013	Cohort study, *N* = 36 CHD	SVA	61%	MRI (structural, MRS)	36% brain injury (4 mild WMI, 4 moderate WMI, 2 severe WMI, 6 focal strokes, 5 IVH) Higher mean average diffusivity for gray matter and lower FA in the white matter regions Lower mean NAA/Cho ratios and higher mean Lac/Cho ratios Delayed microstructural brain development
Park et al[a], *Pediatr Cardiol*, 2006	Case-control study, *N* = 16/15	TGA	U	MRI (structural, MRS)	No abnormal findings on preoperative MRI Altered metabolism in parietal white matter (increased Cho/Cr) and occipital gray matter (increased Cho/Cr and Ino/Cr) Altered metabolism persisted 1 y after ASO in parietal white matter and normalized for occipital gray matter
Miller et al, *Ann Thorac Surg*, 2004	Cohort study, *N* = 10	TGA	U	MRI (structural, MRS)	40% brain injury (stroke or hemorrhage) Higher Lac/Cho Similar NAA/Cho between TGA and healthy controls, but those with brain injury on MRI had lower NAA/Cho 0% focal deficits on neurologic examination Abnormalities in tone or reflexes common in newborns with and without brain injury

TABLE 2 Continued

Study (First Author, Journal, Year of Publication)	Study Design, No. Infants	CHD	Antenatal Diagnosis	Methods	Findings (Compared With Healthy Controls and/or Reference Values, Unless Otherwise Stated)
Mahle et al, *Circulation*, 2002	Cohort study, *N* = 24	Mixed	63%	MRI (structural, MRS)	25% ischemic lesions (small cortical watershed infarct, small infarct of the caudate, PVL) 4% hemorrhagic injury 16% elevated lactate with diffuse distribution, 25% lactate localized to the basal ganglia, 4% lactate in the peri-insular region Elevation of brain lactate associated with brain injury
Dimitropoulos et al, *Neurology*, 2013	Cohort study, *N* = 120	Mixed	33%	MRI (structural, DTI, MRS)	41% brain injury Lower WM FA and lower NAA/Cho associated with higher injury severity preoperatively Higher SNAP-PE, lower Spo_2, hypotension, and BAS predictive for higher injury severity
Shedeed and Elfaytouri, *Pediatr Cardiol*, 2011	Case-control study, *N* = 38/20	Mixed	U	MRI (structural, DTI, MRS)	24% white matter injury (PVL and stroke) Lower NAA/Cho ratio (0.55 vs 0.67) Higher Lac/Cho ratio (0.14 vs 0.09) Higher average diffusivity (1.41 vs 1.27) Lower white matter FA (0.19 vs 0.25)
Miller et al, *N Engl J Med*, 2007	Case-control study, *N* = 41/16	SVA	17%	MRI (structural, DTI, MRS)	32% brain injury Decreased NAA/Cho (10%), increased average diffusivity (4%), decreased FA (12%), increased Lac/Cho (28%)
Nagaraj et al, *J Pediatr*, 2015	Case-control study, *N* = 43/58	Mixed	100%	MRI (structural, ASL)	32.6% brain injury (64.3% WMI) compared with 0.6% in controls All cerebral blood flow parameters lower but not significantly different Lower global cerebral blood flow and regional cerebral blood flow in SVA Lower regional thalamic cerebral blood flow in cyanotic CHD and lower cerebral blood flow in thalami, occipital white matter, and basal ganglia compared with acyanotic CHD
Licht et al, *J Thorac Cardiovasc Surg*, 2004	Cohort study, *N* = 25	Mixed	U	MRI (volume, ASL)	Mean cerebral blood flow 19.7 ± 9.1 mL/100 g per min compared with 50 ± 3.4 mL/100 g per min in controls 5 neonates cerebral blood flow <10 mL/100 g per min (moderate ischemic changes in piglets) 24% microcephaly Low Hb associated with higher baseline cerebral blood flow 28% PVL, associated with lower cerebral blood flow and less reactivity to hypercarbia
Van der Laan et al, *Pediatr Res*, 2013	Retrospective study, *N* = 21 (12 BAS)	TGA	U	NIRS	Preductal Spo_2 increased immediately after BAS (72%–85%) and stabilized afterward (86%) r_cSo_2 increased immediately after BAS and continued increasing during 24 h after BAS (42%–48% 2 h after BAS to 64% 24 h after BAS) Lower baseline r_cSo_2 in the BAS group, whereas post-BAS r_cSo_2 was higher compared with infants who did not undergo BAS (64% vs 58%)
Uebing et al, *J Thorac Cardiovasc Surg*, 2011	Cohort study, *N* = 53	HLHS, TGA	U	NIRS	10 h before surgery, HLHS infants had higher r_cSo_2 than TGA infants (61% vs 56%) In HLHS infants, r_cSo_2 decreased after CPB and recovered to preoperative values within 48 h after CPB In TGA infants, r_cSo_2 decreased after CPB and increased ∼20% above preoperative values within 48 h after CPB
Kurth et al, *Ann Thorac Surg*, 2001	Case-control study, *N* = 91/19	Mixed	U	NIRS	Lower r_cSo_2 (immediately before surgery in the operating room, 1 min recordings) Infants with PA had lowest r_cSo_2 values (38% ± 8%)
Latal et al[a], *Dev Med Child Neurol*, 2015	Cohort study, *N* = 77	Mixed	27%	CUS	29% brain injury (16% brain edema, 6% PVL, 4% ventricular dilatation, 3% IVH grade I) Clinical variables not associated with brain injury BAS associated with brain edema (32% vs 6%)
Gunn et al[a], *Ann Thorac Surg*, 2012	Cohort study, *N* = 39	SVA	95%	aEEG	33% EA, commonly left-sided, predominantly occurring during CPB 0% preoperative EA
Gunn et al[a], *Intensive Care Med*, 2012	Cohort study, *N* = 150	Mixed	U	aEEG	3% preoperative EA

TABLE 2 Continued

Study (First Author, Journal, Year of Publication)	Study Design, No. Infants	CHD	Antenatal Diagnosis	Methods	Findings (Compared With Healthy Controls and/or Reference Values, Unless Otherwise Stated)
Te Pas et al, *Acta Paediatr*, 2005	Retrospective study, *N* = 50	Mixed	U	CUS	42% abnormal CUS (26% widening ventricles or subarachnoidal space, 8% ischemic changes, 6% lenticulostriate vasculopathy) Abnormalities on CUS tended to occur more frequently in HLHS or CoA (63%) than TGA (14%)
Sigler et al, *Ann Thorac Surg*, 2001	Cohort study, *N* = 35	TGA	U	CUS	3% preoperative brain injury (enhanced subependymal echogenicity) 65% resolved within 2 wk after operation Neuron specific enolase not associated with brain injury
Combination of techniques					
Mulkey et al, *Pediatr Neurol*, 2015	Cohort study, *N* = 24	Mixed	100%	aEEG MRI (structural)	63% abnormal aEEG (42% mildly abnormal, 21% severely abnormal) Abnormal aEEG associated with lower Apgar score at 5 min, CHD surgery at an older age, and male sex 50% brain injury (infarct and/or white matter injury) Infants with brain injury higher odds of having abnormal aEEG (OR = 3.0) 33% brain atrophy Severely abnormal aEEG background pattern associated with brain atrophy (OR = 15.0)
Dehaes et al, *Biomed Opt Express*, 2015	Case-control study, *N* = 11/13	SVA	U	NIRS DCS	Lower cerebral oxygen metabolism index, cerebral blood flow index, cerebral oxygen saturation index, and hemoglobin Higher cerebral oxygen extraction
Jain et al, *J Cereb Blood Flow Metab*, 2014[12]	Cohort study, *N* = 32	Mixed	U	MRI DOS (NIRS) DCS	Lower resting state oxygen extraction fraction, cerebral blood flow, and cerebral metabolic rate for oxygen
Lynch et al, *J Thorac Cardiovasc Surg*, 2014	Cohort study, *N* = 37	HLHS	U	MRI (structural) DOS (NIRS) DCS	22% PVL Longer time to surgery associated with postoperative PVL Lower r_cSo_2 and higher blood flow index associated with postoperative PVL Longer time to surgery associated with lower r_cSo_2 and higher FTOE
Rios et al, *Pediatrics*, 2013	Cohort study, *N* = 167	Mixed	U	MRI (structural) CUS	3% brain injury ultrasound (4 hemorrhage, 1 PVL) 26% brain injury MRI (WMI most common) 4 infants with hemorrhage on CUS had normal MRI suggesting 80% false positives and a positive predictive value for brain injury of only 20% for HUS before surgery
Andropoulos et al[a], *Ann Thorac Surg*, 2012	Cohort study, *N* = 30	Mixed	43%	MRI (structural) NIRS	33% brain injury Mean preoperative r_cSo_2 56.5% (53.0%–61.9%) r_cSo_2 < 45% area under the curve 9 (0–191) min
Williams et al[a], *Ultrasound Obstet Gynecol*, 2012	Pilot study, *N* = 13	Mixed	100%	Ultrasound (Doppler) EEG	MCA-PI −0.75 TGA, −2.01 TOF, −2.4 HLHS CPR < 1 40% TGA, 67% TOF, 60% HLHS MCA-PI positive correlation with neonatal EEG left frontal polar and left frontal β power CPR < 1 associated with lower left frontal polar en left frontal β power
Ter Horst et al, *Early Hum Dev*, 2010	Cohort study, *N* = 62	Mixed	15%	aEEG CUS	40% normal aEEG, 45% mildly abnormal (DNV), 15% severely abnormal (BS, CLV, FT) Similar rate of severely abnormal aEEG in cyanotic and acyanotic CHD (13% vs 16%) 19% EA, more frequently observed in acyanotic CHD (OR 9.37) 58% SWC within 72 h In acyanotic CHD, SWC more frequent in CoA than in HLHS (92% vs 48%) 9% ischemia on HUS Trend for more severely abnormal background patterns in abnormal HUS (OR 5.4) Severely abnormal background pattern and EA associated with more profound acidosis (low pH, more negative base excess, higher lactate)
McQuillen et al, *Stroke*, 2007	Cohort study, *N* = 62	Mixed	U	MRI (structural) NIRS	39% preoperative brain injury (18% WMI, 21% stroke, 8% IVH) Risk factors for preoperative brain injury: BAS and 5 min Apgar score Preoperative brain injury more common in 2 ventricle anomalies
Toet et al[a], *Exp Brain Res*, 2005	Cohort study, *N* = 20	TGA	U	NIRS aEEG	Lower r_cSo_2 (27%–52%) 12 h before CPB 100% normal aEEG, 0% EA No difference in duration to normalization in aEEG after surgery between preoperative low or high r_cSo_2

TABLE 2 Continued

Study (First Author, Journal, Year of Publication)	Study Design, No. Infants	CHD	Antenatal Diagnosis	Methods	Findings (Compared With Healthy Controls and/or Reference Values, Unless Otherwise Stated)
Robertson et al[a], *Cardiol Young*, 2004	Cohort study, *N* = 47	Mixed	U	EEG CUS	11% preoperative abnormal EEG (2.8% clinical seizure) Nadir CBF velocity 2 h post CPB No association between CBF velocity and EEG

ASL, arterial spin labeling; ASO, arterial switch operation; BS, burst suppression; CLV, continuous low voltage; CoA, coarctation of the aorta; CPB, cardiopulmonary bypass; CUS, cranial ultrasound; DCS, diffuse correlation spectroscopy; DNV, discontinuous normal voltage; DTI, diffusion tensor imaging; DTT, diffuse tensor tractography; FA, fractional anisotropy; FT, flat trace; FTOE, fractional tissue oxygen extraction; GA, gestational age; IVH, intraventricular hemorrhage; Ino/Cr, myo-inosinotol/creatinine; MRS, magnetic resonance spectroscopy; OR, odds ratio; PVL, periventricular leukomalacia; SNAP-PE, Score for Neonatal Acute Physiology–Perinatal Extension; SpO_2, pulse oxygen saturation; SVA, single ventricle anomaly; SWC, sleep-wake cycling; TOF, tetralogy of Fallot; U, unknown; WMI, white matter injury.

[a] Articles that also address neurodevelopmental outcome.

still present in the white matter and disappeared in the gray matter 1 year after the arterial switch operation.[48]

Apart from delayed cerebral development, the most commonly observed lesions on MRI were (punctate) white matter injury, periventricular leukomalacia, and stroke. Such brain lesions were reported in 19% to 52% of the cases.[31,46,50–69] Although the type of CHD was associated with the occurrence of developmental delay or brain injury on MRI, most studies did not specify these differences.[39–41,45]

There were multiple clinical factors associated with preoperative brain injury. Risk factors for preoperative brain injury included brain immaturity,[53,54,59,64,70] lower arterial oxygen saturation values,[53,63,71,72] lower Apgar scores at 5 minutes,[56,61,70] abnormal amplitude-integrated electroencephalography (aEEG) background pattern,[65] longer time to surgery,[72] male sex,[73] and presence of brain lactate.[74] A higher Score for Neonatal Acute Physiology–Perinatal Extension, hypotension, lower white matter fractional anisotropy, and lower NAA/Cho were associated with higher brain injury severity.[53] Balloon atrial septostomy (BAS) was found to be an independent risk factor for brain injury in 4 studies,[53,58,61,70] whereas 4 other studies did not find an association between BAS and brain injury.[54,60,71,72]

Near-Infrared Spectroscopy

Only a few studies examined regional cerebral oxygen saturation (r_cSo_2) by means of near-infrared spectroscopy (NIRS) before surgery. Neonates with CHD had significantly lower preoperative r_cSo_2 compared with healthy controls.[75–77] Neonates with HLHS had higher r_cSo_2 than neonates with TGA,[78] and neonates with a pulmonary atresia (PA) had the lowest r_cSo_2.[75] In HLHS, neonates in whom cerebral oxygen saturation was monitored by NIRS had higher arterial oxygen saturation, were less often mechanically ventilated, and were less often intubated for a presumed circulatory mismatch.[79] In TGA, r_cSo_2 increased immediately after BAS and continued increasing during the 24 hours after BAS. Neonates in need of BAS had lower baseline r_cSo_2 but higher post-BAS r_cSo_2 compared with neonates who did not undergo BAS.[80]

Other Techniques

Brain injury on transcranial ultrasound was reported in up to 42% of the cases. The positive predictive value of transcranial ultrasound for the presence of brain injury, however, was very low with a value of 20%.[81–84]

Up to 63% of the neonates had an abnormal preoperative aEEG recording (42%–45% mildly abnormal and 15%–21% severely abnormal).[65,85–87] In 0% to 19% of the cases, epileptic activity (EA) was registered[65,85–87] before surgery. EA was more frequently observed in neonates with acyanotic CHD.[85] An abnormal aEEG recording was associated with lower Apgar scores at 5 minutes, surgery at an older age, and male sex.[65] Furthermore, neonates with brain injury had higher odds of having abnormal aEEG recordings.[65]

Neurodevelopmental Outcome in Infants With CHD

Sixteen prenatal or preoperative postnatal studies reported on NDO in infants with CHD. Fourteen of these studies used the BSID II or Bayley III at an age of 6 to 48 months. Thirteen studies assessed the association between prenatal or preoperative postnatal cerebral findings and NDO and were included in Table 3. Although scores were frequently within the normal range reported in healthy term infants (mean, SD 100 ± 15), almost all studies reported poorer NDO scores in infants with CHD compared with healthy controls or normative data. For the BSID II, the psychomotor developmental index (PDI) was more affected than the mental developmental index (MDI). Mean composite scores for the PDI ranged from 69.0 to 103.0 in infants with CHD[14,24,81,88,89] and for the MDI from 85.2 to 103.5.[14,24,81,88,89] The mean composite scores for the Bayley III were slightly higher compared with the composite scores for the BSID II. Mean cognitive scores ranged from 91.0 to 104.8, mean language scores ranged from 87.8 to 97.0, and mean motor scores ranged from 86.0 to 97.0.[37,52,54,62,85,86]

There were many prenatal and postnatal preoperative factors

TABLE 3 Prenatal and Preoperative Cerebral Findings and Their Relation With NDO

Study (First Author, Journal, Year of Publication)	Study Design, No. Infants	CHD	Age at NDO Testing, Mo	Methods	Outcome	Findings (Compared With Healthy Controls and/or Reference Values, Unless Otherwise Stated)	Relation
Ultrasound							
Hahn et al, *Ultrasound Obstet Gynecol*, 2016	Retrospective study, *N* = 133	SVA	14	Ultrasound (Doppler and biometry)	BSID II	MDI 88.5 ± 16.6 and PDI 76.4 ± 19.8 First MCA-PI negatively associated with PDI HC/AC negatively associated with PDI	±
Zeng et al, *Ultrasound Obstet Gynecol*, 2015	Case-control study, *N* = 112/112	Mixed	12	Ultrasound (three dimensional, Doppler)	BSID II	Lower MDI (85.2 vs 99.1) and PDI (72.8 vs 99.4) No correlation between MCA-PI and NDO Total intracranial flow index positively correlated with PDI and MDI	±
Williams et al, *Am Heart J*, 2013	Cohort study, *N* = 134	SVA	14	Ultrasound (Doppler)	BSID II	MDI 88.5 ± 16.6 and PDI 76.4 ± 19.8 62% PDI < 85 and 35% MDI < 85 MCA-PI correlated negatively with PDI but not with MDI MCA-PI < −2.0, on average, with 11-point-higher PDI scores compared with MCA-PI > −2.0 (84.7 vs 73.6)	+
Latal et al, *Dev Med Child Neurol*, 2015	Cohort study, *N* = 77	Mixed	12	HUS	BSID II	MDI 89 (49–107) and PDI 69 (49–113) Isolated CHD: MDI 91 (50–107) and PDI 70 (49–113) No association between brain injury on ultrasound and NDO	−
MRI							
Masoller et al, *Ultrasound Obstet Gynecol*, 2016	Case-control study, *N* = 58/58	Mixed	6	MRI	Bayley III	Lower cognitive (91 vs 103), language (97 vs 108), motor (86 vs 100), social-emotional (85 vs 106), and adaptive (89 vs 97) score Average Bayley III score associated with total blood volume, left and right singulate depth, frontal Ino/Cho ratio, and NAA/Cho ratio	+
Andropoulos et al, *Paediatr Anaesth*, 2014	Retrospective study, *N* = 59	Mixed	12	MRI	Bayley III	Composite scores: cognitive 102 ± −13.3, language 87.8 ± −12.5, motor 89.6 ± 14.1 Preoperative brain injury not associated with NDO Preoperative r_cSo_2 values associated with cognitive and motor score	±

TABLE 3 Continued

Study (First Author, Journal, Year of Publication)	Study Design, No. Infants	CHD	Age at NDO Testing, Mo	Methods	Outcome	Findings (Compared With Healthy Controls and/or Reference Values, Unless Otherwise Stated)	Relation
Beca et al, *Circulation*, 2013	Cohort study, *N* = 153	Mixed	3 and 24	MRI	Bayley III	Composite scores: cognitive 94 ± 15, language 94 ± 16, motor 97 ± 12 Delay in maturation of the posterior limb of the internal capsule on the first MRI associated with lower motor scores Lower brain maturity associated with reduced performance on all domains	+
Amplitude-integrated EEG							
Gunn et al, *Ann Thorac Surg*, 2012	Cohort study, *N* = 39	SVA	24	aEEG	Bayley III	Composite scores: cognitive 92.4 ± 13.5, language 94.3 ± 17.7, motor 93.8 ± 10.6 Seizures associated with mortality but not associated with NDO Recovery of background pattern within 48 h: 14 points increase in motor score	±
Gunn et al, *Intensive Care Med*, 2012	Cohort study, *N* = 150	Mixed	48	aEEG	Bayley III	Composite scores: cognitive 93.2 ± 13.7, language 93.5 ± 16.2, motor 96.7 ± 12.7 Preoperative background pattern not associated with NDO	–
Combination of techniques							
Andropoulos et al, *Ann Thorac Surg*, 2012	Cohort study, *N* = 30	TGA	12	NIRS	Bayley III	Composite scores: cognitive 104.8 ± 15, language 90.0 (83.0–94.0), motor 92.3 ± 14.2	+
				MRI		Lower preoperative r_cSo_2 associated with lower cognitive score Preoperative brain injury associated with lower language score Preoperative brain injury, lower preoperative r_cSo_2, associated with lower motor score	

TABLE 3 Continued

Study (First Author, Journal, Year of Publication)	Study Design, No. Infants	CHD	Age at NDO Testing, Mo	Methods	Outcome	Findings (Compared With Healthy Controls and/or Reference Values, Unless Otherwise Stated)	Relation
Williams et al, *Ultrasound Obstet Gynecol*, 2012	Pilot study, *N* = 13	Mixed	18	Ultrasound (Doppler) EEG	Bayley III	Composite scores: cognitive 95, language 84, motor 87 Language and motor scores in HLHS and TOF >1 SD below population mean MCA-PI correlated positively with cognitive scores EEG left frontal polar and left frontal β power correlated positively with cognitive scores MCA-PI correlated positively with neonatal EEG left frontal polar and left frontal β power	+
Toet et al, *Exp Brain Res*, 2005	Cohort study, *N* = 20	TGA	30	NIRS aEEG	BSID II	$r_cSo_2 \leq 35\%$: MDI 97 and PDI 95 $r_cSo_2 > 35\%$: MDI 101 and PDI 106 Low r_cSo_2 associated with lower MDI and PDI	±
Robertson et al, *Cardiol Young*, 2004	Cohort study, *N* = 35	Mixed	12	BSID II EEG Transcranial Doppler	BSID II	Preoperatively: MDI 103 ± 5 (all infants within normal range) and PDI 99 ± 8 (2 infants below 80) 12 mo follow-up: MDI 94 ± 13 and PDI 89 ± 20 57% both MDI and PDI in normal range No association between EEG abnormalities, reduced cerebral blood flow, and NDO	–

HC/AC, head circumference/abdominal circumference; SVA, single ventricle anomaly; TOF, tetralogy of Fallot.

associated with neurodevelopmental outcome in infants with CHD. Two articles found a negative correlation between MCA-PI and NDO.[24,88] MCA-PI < 2.0 was associated with an increase of PDI of 11 points.[88] One article found a positive correlation between MCA-PI and Bayley III cognitive scores[16] and 1 article did not find any association between MCA-PI and NDO.[14] A delayed development of the cerebrum was also associated with poorer NDO.[38,54] Preoperative brain injury on MRI was associated with lower language and motor scores,[62] whereas brain injury on preoperative ultrasound was not associated with NDO.[81] Lower preoperative r_cSo_2 was associated with lower cognitive scores and lower motor scores[62] and with lower BSID II scores.[76]

There was little evidence on the association between preoperative EEG or aEEG and NDO. One study found a positive association between preoperative left frontal polar and left frontal β power and cognitive scores.[16] Three other studies did find an association between intraoperative or postoperative aEEG and NDO, but not between preoperative aEEG and NDO outcome.[85,86,88]

DISCUSSION

This systematic review demonstrates that prenatal and postnatal preoperative brain injury are common in infants with CHD. More importantly, this review demonstrates that abnormal cerebral findings during these periods might be associated with poorer neurodevelopmental outcomes in later life.

One major finding of this review was the presence of cerebral developmental delay in many infants with CHD during both the prenatal as well as the postnatal preoperative period. All cerebral regions were affected and a delay of up to 4 weeks compared with healthy controls was described.[49] It has been well established that preterm-born infants are at risk for developing brain injury because of the complex mechanisms of destructive events and developmental issues. The preterm brain is associated with vulnerable white matter, immature vasculature, and impaired autoregulation.[90] Moreover, signs of cerebral developmental delay are associated with adverse NDO in preterm infants. In infants with CHD, cerebral developmental delay was associated with the occurrence of brain injury on preoperative MRI and also with the severity of brain injury.[53,59,64] We speculate, therefore, that cerebral developmental delay might lead to an increased vulnerability of the brain and could therefore be an important contributor to brain injury in infants with CHD.

Another major finding was that many fetuses with CHD had abnormal Doppler parameters. PI of the middle cerebral artery and CPR were low, whereas UA-PI was high compared with healthy fetuses in the majority of studies that reported on Doppler parameters. These findings are in accordance with redistribution of blood flow to enhance cerebral perfusion, also called the brain-sparing effect.[30] Brain sparing might be a consequence of low cerebral oxygen content (hypoxemia) or low cerebral blood volume (ischemia). In fetuses with intrauterine growth restriction, brain sparing is a sign of severely impaired oxygen and/or nutrient supply and is associated with mortality and poor outcome.[91] In fetuses with CHD, this association seems to be less clear[8,14,16,24,88] and might even be a protective factor.[24,88] Moreover, it has been reported that up to 23.8% of fetuses with CHD are also growth restricted,[92–94] and variable degrees of impaired placental function may concurrently modulate cerebral vascular resistance. Brain sparing in fetuses with CHD could be an adaptive mechanism to compensate for either hypoxemia (low Po_2 because of placental insufficiency), hypoxia (low oxygen saturation because of intra- and extracardiac mixing), or ischemia.[95] In all 3 situations, changes in cerebral vascular resistance may occur to compensate for poor oxygenation and to meet cerebral metabolic demands.[14] Unfortunately, to date there are no studies looking systematically at uteroplacental (UA) and fetal (MCA, ductus venosus) flow to clarify if and to what extent brain sparing is determined by the effect of the cardiac lesion on oxygen saturation in fetuses with CHD.

Postnatally, brain injury was frequently reported (up to 52%) before cardiac surgery in infants with CHD. The most commonly observed lesions were all associated with decreased cerebral blood flow (ischemia) and included (punctate) white matter injury, periventricular leukomalacia, and stroke.[30] Another indicator of an ischemic state was the presence of cerebral lactate in some infants with CHD.[34,74] In addition to ischemia, hypoxia might also play a role in the development of early acquired brain injury in infants with CHD. Multiple studies found low arterial oxygen saturation values to be an independent risk factor for preoperative brain injury and high arterial oxygen saturation values to be a protective factor for preoperative brain injury.[53,58,61,71,72]

In general, infants with CHD scored lower on neurodevelopmental tests compared with healthy infants. Their mean scores, however, were frequently within the normal ranges reported in healthy term infants (mean, SD 100 ± 15). A possible explanation for these normal scores might be that most infants were examined during early childhood (6–48 months). Certain capacities and skills such as memory function and abstract-logic thinking mature during the course of childhood, and problems might only become apparent at an older age.[96] Children with CHD at school age on average score lower on motor skills, higher-order language, visual-spatial skills, vigilance, and sustained attention. These deficits often persist through adolescence into adulthood. Furthermore, children and adolescents with complex CHD often have difficulties with social cognition and executive functioning, which might lead to psychosocial disorders and a lower quality of life.[97]

We found numerous associations between prenatal and postnatal preoperative cerebral findings and neurodevelopmental outcome in infants with CHD. Both prenatally as well as postnatally we were unable to identify specific cerebral findings that were responsible for poorer neurodevelopmental functioning in infants with CHD. We speculate, therefore, that neurodevelopmental impairment in CHD is the cumulative effect of delayed microstructural development in combination with multiple hypoxic and/or ischemic events during prenatal and postnatal preoperative life rather than being caused by a single independent factor.

Research to further clarify the actual mechanisms responsible for neurodevelopmental impairment in infants with CHD is essential. Nowadays, the adult population with CHD is larger than the pediatric population with CHD. Many adults with CHD still experience psychosocial and cognitive challenges that may impact emotional functioning, academic achievement, and even

quality of life.[98–101] To explore pathophysiological mechanisms and to optimize treatment protocols, large (multicenter) prospective trials should be conducted that include the prenatal to the postoperative period with an adequate duration of follow-up. Furthermore, increasing awareness of the vulnerability of the young developing brain of an infant with CHD is also essential among physicians and other caregivers that are involved in the treatment to prevent neurodevelopmental impairment later in life.

This systematic review has several limitations. First, most studies included in this review were observational studies. This type of study is unequivocally associated with a risk of bias of under- or overestimating outcome measures. The vast majority of studies, however, were of reasonable to very good quality according to the Newcastle-Ottawa Quality Assessment Scale. Second, comparisons between studies were difficult because various techniques and methods were used to assess cerebral abnormalities in infants with complex CHD. Reference values for antenatal Doppler parameters, for example, were different from one study to another. In addition to various techniques and methods, numerous different types of CHD were included with different pathophysiology, circulatory effects, and treatment protocols. This also made comparisons between studies more difficult. Future studies should differentiate between cardiac lesions to make risk stratification of infants with CHD possible and counseling perhaps a little more specific.[102] Finally, an effect of chromosomal abnormalities on cerebral development and NDO cannot be ruled out completely since not all studies stated whether they included infants with chromosomal abnormalities with CHD. For future studies, it would also be interesting to assess differences in cerebral abnormalities and NDO between infants with isolated CHD and infants with nonisolated CHD.

CONCLUSIONS

The current systematic review suggests that prenatal and postnatal preoperative abnormal cerebral findings may play an important role in neurodevelopmental impairment in infants with CHD. Physicians and other caregivers should be more aware of this vulnerability of the brain and of the possible effect repeated episodes of hypoxia and/or ischemia during early life may have in infants with CHD. Prenatal and postnatal counseling remains challenging when CHD is diagnosed.[102] Targeted investigation in each individual case may help clarify which injuries are already present prenatally and which are due to the postnatal course of the condition.

ABBREVIATIONS

aEEG: amplitude-integrated electroencephalography
BAS: balloon atrial septostomy
Bayley III: Bayley Scales of Infant and Toddler Development III
BSID II: Bayley Scales of Infant Development II
CHD: congenital heart disease
Cho/Cr: choline/creatinine
CPR: cerebroplacental ratio
EA: epileptic activity
HC: head circumference
HLHS: hypoplastic left heart syndrome
Ino/Cho: myo-inositol/choline
Lac/Cho: lactate/choline
MCA: middle cerebral artery
MCA-PI: pulsatility index of the middle cerebral artery
MDI: mental developmental index
NAA/Cho: n-acetylaspartate/choline
NDO: neurodevelopmental outcome
NIRS: near-infrared spectroscopy
PA: pulmonary atresia
PDI: psychomotor developmental index
PI: pulsatility index
r_cSo_2: cerebral oxygen saturation
TGA: transposition of the great arteries
UA: umbilical artery
UA-PI: pulsatility index of the umbilical artery

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