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Characterization of Lesions in the Central Nervous System Based on Neurosonography and Magnetic Resonance in Fetus with Isolated Congenital Heart Defects. A Systematic Review

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Abstract

Introduction: Congenitalheartdefectsrepresentoneofthemainmalformationsdiagnosed prenatally. These are a major cause of neuro developmental disorders and it has even been proposed that structural brain alteration is found from early stages of fetal development.

Objective: The objective of this study was to review the existing evidence of prenatal diagnosis of structural braina lterations found in fetal brain magnetic resonance imaging and neurosonography in fetus with isolated congenital heart defect.

Materials and Methods: A search of Pubmed, Science Direct, Clinical Key and EBSCO databases was conducted in order to review study cases of fetuses with congenital heart defect between 18 and 37 week with Doppler ultrasonography, neurosonography and /or fetal brain magnetic resonance imaging.

Results: A total of 16 articles were selected and it was found that the fetuses with congenital heart defect present structural neurological alterations from intrauterine life showed by neurosonography and fetal brain magnetic resonance imaging.

Conclusion: The evidence emphasizes on the importance of studying in detail the central nervous system of fetuses with congenital heart defect and the relationship between structural brain alterations and neurodevelopmental disorders impairment since prenatal stages.

Keywords: Congenital heart defect, Fetal magnetic resonance, Neurosonography, Structural neurological alterations, Neurodevelopment.

Introduction

Congenital heart defects(CHD) represent one of the mainmal formations diagnosed prenatally, affecting upto1% of pregnancies.[1,2] These are a major cause of neuro developmental disorders (ND) that can be evidenced in the early years of childhood.[3] ND alteration soccur in approximately 50% of live newborns with mod-

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erate to severe CHD diagnosed prenatally.[4-7] However, the specific prenatal causes and the mechanisms of insult are largely unknown and it isnotyetclearifthestructuralbrainalterationsinfetuseswithisolated CHD evidenced in Doppler ultrasonography and magnetic resonance imaging (MRI) of the brain are directly related to ND alterations.[6,8] In fetal brain MRI, brain abnormalities appear with a prevalence of 39%.[9] Brain structural changes and ND alteration occur in different stages in both prenatal and postnatal l life and have been demonstrated by several studies.[10] However, the number of studies that demonstrate the previous argument sin sufficient.[3,5] There search focused on the alterations that occurred the corrective surgery and cardiopulmonary bypass with a perioperative perspective. Nevertheless, it was found that more than half of the children had cognitive and structural deficiencies prior to the surgical procedure, which is why it is raised with more evidence that central nervous system alterations occur since intrauterine life.[9,11,12] It has been proposed that intrauterine structural brain alteration in fetuses with CHD occur prior to ND alteration.[13,14] Frequent findings are white matter alterations, cortical maturation, strokes, hemorrhages and functional alterations before cardiac surgery.[12,15] Considering that the cognitive development disorders have a prevalence of around 1% in developed countries and 2% in developing countries, it is important the diagnosis of structural and functional alterations of the brain parenchyma in the prenatal stage. The latter would facilitate a proper monitoring and timely intervention. Consequently, this will allow providing adequate counseling to families and achieving early interventions within the first years of life, which are crucial for ND. The objective of this systematic review was to analyze the existing evidence regarding the prenatal diagnosis of structural brain alterations evidenced in MRI and neurosonography (NS) in fetuses with congenital heart defect.

Materials and Methods

Design

Systematic literature search

Types of study to include

All epidemiological study designs were included with the exception the series and case reports.

Population

Fetuses with ultrasound diagnosis of CHD between 18 and 37 weeks of gestation without chromosomic alterations or associated extra cardiac malformations and with Doppler ultrasonography, NS and fetal brain magnetic resonance imaging.

Types of diagnostic tests

Fetal brain magnetic resonance imaging, ultrasound, feto placental Doppler

Search methods to identify the studies: Electronic searches: We identify the studies that meet the in clusion criteria in English or Spanish. We use a set of controlled and uncontrolled terms for "Fetus", "Fetal", "Heart Defects", "Congenital", "Magnetic Resonance Imaging", "Neurological structure", "Nervous system structure" and "Neuro developmental Disorders", with field labels (title and abstract), proximity operators and Boolean operators. The search strategies are found in Annex1.

Specifically we use the following data bases:

- The Cochrane Central Register of Controlled Trials
- (CENTRAL, Ovid platform): inception to present.
- MEDLINE®, Ovid platform: inception to present.
- MEDLINE® In-Process & Other Non-Indexed Citations,
- Ovid platform: inception to present.
- MEDLINE® Daily Update, Ovid platform: inception to present.
- EMBASE, embase. Com platform: inception to present.
- LILACS, IAH xinterface: inception to present.

Data collection and analysis

Selection of studies

Two authors considered the inclusion and exclusion criteria of all the titles and abstracts found in the search strategy and carried out a qualitative analysis of them. All the potentially relevant studies were evaluated in full text. The entire selection process was documented in a PRISMA flow diagram.

Data extraction and management

An extraction format was designed and an author will collect the following information of each reference:

- Study design
- Year of publication
- Participants: characteristics
- Number of participants in each group
- Losses in the monitoring
- Tests used
- Definition and frequency of outcomes in each group

Risk of bias assessment

The authors independently assessed the risk of bias included according their designs. For randomized studies we will use the risk of bias assessment of Cochrane Collaboration. For observational studies we will use the Joanna Briggs Institute Check list.

Results

Search results

Having into account the research question, a literature search was conducted finding 330 articles, of which 30 articles were ruled out for duplication, 277 for not answering their search question when reviewing the title and the abstracts, 1 for being a case report and 6 for being systematic reviews, leaving a total of 16 studies for the review (n=912cases) Figure 1:

- 6 case studies and controls (n=214cases)
- 9 cohort studies (n=565 cases)
- 1clinic altrial (n=133cases)

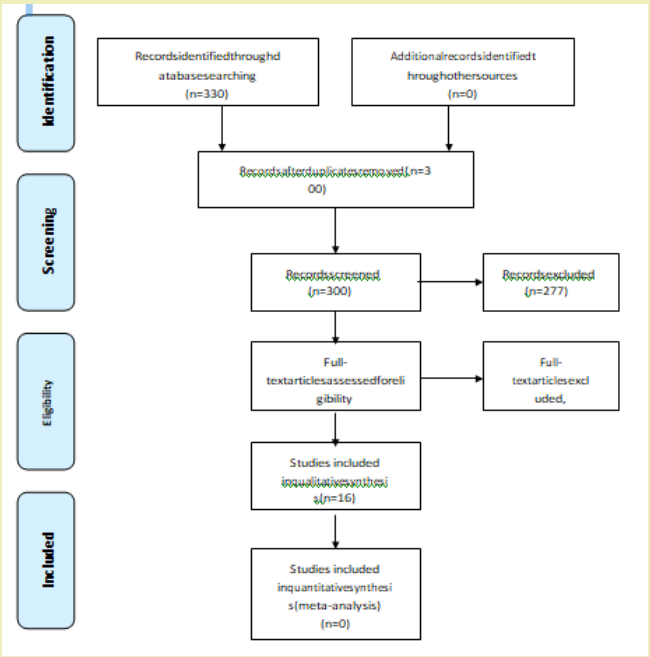

Figure 1: PRISMA Flow Diagram.

Studies out comes

For the qualitative analysis of the studies that met the inclusion criteria (16 studies), they were grouped by study type.

Case-control studies (n=6)

The case-control studies had in common the search for the association between alterations in brain growth (structural and functional) and CHD. It is increasingly recognized that the brain is abnormal in many newborns with CHD, which was previously attributed exclusively to postnatal cardiac surgery.[9,11,12] Several theories have been proposed to explain the correlation between CHD and fetal ND alterations; however, it is not yet clear if these neurological structural alterations are found in all fetuses with CHD, in addition, if these are directly related to the ND alterations.[6,8,16-18] Studies have found neurological alterations in utero with the use of fetal brain magnetic resonance imaging. Weissmann-Brenner A[19] in their case-control study they report significantly higher rates of general cerebral, ventricular and cortex pathologies and altered biometric parameters in the cyanotic CHD group compared to the control group.[19] The results suggest a pathogenesis in the uterus of the neurological and cognitive abnormalities found during childhood development. In the evaluation of neurological development, cerebral cortical development and regional growth of brain tissue have been studied as early and sensitive markers of brain growth failure in this and other high-risk populations. Similarly, Clouchoux Cetal,[13] found that the volumes of white and gray matter were significantly lower in the group of Hypoplastic Left Heart Syndrome(HLHS) vs controls (p value<0.001), with a difference that became progressively higher after 30 weeks of gestation (GA).[13] This study reports for the first time in vivo cortical development in fetuses with HLHS, finding that the cingulate sulcus was visible in controls from 25 GA, but not until 28 GA in fetuses with HLHS; the superior frontal sulcus was visible from 27 GA in control fetuses, but not until 30 GA in HLHS fetuses; likewise, the anterior ascending limb was visible from week 32 to 33 GA in controls, but only until 36GA in fetuses with HLHS. However, in this study, only fetuses with HLHS were evaluated, which prevents extrapolating the results too ther types of heart diseases. Previously, Limperopoulos C[6] reported brain growth and metabolism between normal fetuses and those with CHD, with the use of three-dimensional volumetric magnetic resonance imaging (MRI) and proton magnetic resonance spectroscopy (H-MRS).[6] This study found that brain volume and metabolism are abnormal in third trimester fetuses with some forms of CHD, particularly those with HLHS, transposition of the great arteries (TGA), and reduced flow through the systemic ventricle or antegrade around the aortic arch. In addition, quantitative magnetic resonance imaging provided deeper information about the timing of abnormalities that could disrupt normal fetal brain development. This study found that control fetuses had linear relationships between total brain volume (TBV) and GA (p value<0.001). Similarly, linear relationships between intracranial cavity volume (ICV) and GA (p value<0.001) with progressive increases in TBV and ICV during the third trimester. TBV and ICV were progressively smaller in fetuses with CHD relative to controls (p value<0.001). This shows that fetuses with some forms of CHD have smaller total brain volumes than normal fetuses during the third trimester, a critical period of development during which there is generally an acceleration of brain growth, which requires a lot of energy. Likewise in the Sun L[20] study, Magnetic Resonance and Doppler echocardiography studies have confirmed fetal blood flow abnormalities and decreased oxygen delivery, leading to the immaturity of the developing brain. This study evaluated the direct link between decreased brain oxygenation and impaired brain growth in fetuses with CHD, finding an average 32% reduction in brain oxygen consumption in fetuses

with CHD (p value<0.001), associated with a 13% mean reduction in brain volume (p value<0.001) and a reduction of the complete standard deviation in the estimated Z score of brain weight (p value<0.001), as well as a lower brain volume in all CHD compared to controls.[20] Are duction in venous umbilical oxygen content was evident in fetuses with CHD (p value<0.001), and a failure in oxygen transport from the placenta to the ascending aorta, with a decrease in oxygen saturation fetal brain of 10% (p value<0.001), a mean 6% reduction in umbilical vein oxygen saturation (p=0.0004), which was associated with a mean reductionof17% in delivery of oxygen to the fetal circulation.[20] The Masoller N[7] study was a case-control study that likewise evaluated the associations between CHD, head biometry, and cerebrovascular blood flow dynamics at the time of CHD diagnosis, in the second trimester of pregnancy.[7] In this it was found that a high proportion of fetuses with CHD had a smaller head and still a greater cerebral perfusion in the second trimester of pregnancy. This suggests an early onset of the mechanisms that lead to poorer neurological development later in life. The parameters they evaluated were: biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC) and length of the femur (FL). Cerebral perfusion was evaluated using the middle cerebral artery pulsatility index (MCA-PI), the cerebro placental ratio (CPR) and the fractional moving blood volume (FMBV). These fetuses with CHD showed significantly lower MCA PI and CPRZ scores (−0.23vs.0.34 and−0.37vs.0.30, respectively; p value<0.001) as well as higher FMBVZ score (2.35vs.0.15; p value<0.001). The FMBV>95th percentile was observed in 81.1% of the cases compared to10.5% in controls (p value<0.001), the cases showed a significantly lower Z score of the DBP and HC (P<0.001), in addition a higher proportion of BPD and HC measurements below the 5th percentile compared to controls (51.6% vs. 13.7% and 26.3% vs. 4.2%, respectively; both p value<0.001). This study also found that fetuses with tetralogy of Fallot (TOF) have lower growth rates of the head and estimated fetal weight (EFW), compared to fetuses with HLHS or TGA type CHD. Results similar to those found in the study by Schellen C,[21] which identified early changes in the volumes of the fetal total brain (TBV), gray matter (GMV) and subcortical brain (SBV) in fetuses with TOF.[21] They also found that the TBV was significantly lower (p value<0.001) in the cases of early TOF (<25 of GA) and late. Additionally, the GMV to SBV ratio decreased in TOF fetuses (p value=0.026) compared to normal fetuses, and ventricular volume (p value=0.0048) as well as external cerebrospinal fluid increased in relation to head size (p value<0.001). They concluded that fetuses with TOF have smaller volumes of gray and white matter, with enlarged spaces of cerebro spinal fluid.

Cohort studies (n=9)

In the analysis of the cohort studies we found results similar to those found in the case-control studies in six of the nine studies. The study by Williams IA[22] evaluated the differences in growth between fetuses with and without CHD and the association between growth and early infant ND.[21,22] The results of this study demonstrate that fetuses with CHD had lower growth rates compared to controls (see parameters evaluated and evaluation periods in Table 1, this difference being more notable for HC. Fetal biometry variables that were correlated with cognitive score included: AC at 18-26 GA (p value=0.049) and the HC/AC ratio at 18-26 GA (p value=0.02). The language score was significantly correlated with the FL/BPD ratio at 27-33 GA (p value=0.037) and with the HC/AC ratio (p value=0.045). Motor score was not correlated with any biometric variable. These results demonstrated that fetuses with CHD have lower growth rates compared to controls, mainly for HC. Similar results were found in the Masoller N[7] study, where they report that fetuses with CHD had DBP and HC in percentiles <5 for gestational age.[23] In this study, furthermore, it was shown that fetuses with CHD had significantly lower Z scores for MCA-PI and CPR and a higher Z score for FMBV compared to controls. These same authors previously reported (2015) that fetuses with CHD showed significant changes in brain development, being higher in fetuses with CHD associated with a severe reduction in cerebral oxygenated blood supply, suggesting that this reduction is related to severity of ND deterioration.[24] Olshaker H[25] reported that fetuses with CHD had smaller cerebellar volumes than healthy fetuses, so they suggested additional research in this group of patients as aradiological marker for long-term out come.[25]

In the study by Ortinau C[4] it was demonstrated that fetuses with CHD hadaltered global sulcal patterns in the left hemisphere compared to normal fetuses (p value=0.002).[4] This same group in the same year, reported that infants with CHD had a smaller brain volume before being taken to surgery (p value<0.001) in the same way in the MRI at 3 months (p value=0.0001).[26] In the previously mentioned studies, it is demonstrated that the alteration of the cerebral structural development in fetuses with CHD can have a prenatal origin, being an important predictor of adverse neuro developmental results. However, the sensitivity and specificity of magnetic resonance imaging of the fetal brain to predict neonatal brain injury is currently unknown. Mlczoch E[10] identified the type and incidence of fetal brain pathology in fetuses with prenatal diagnosis of CHD, finding congenital brain disease in 39% of the fetus cohort of the CHD study. However, this study reports limited data on available outcomes.[10] Subsequently, M Brossard Racine[27] showed that the cerebral anomalies detected in the MRI were significantly more frequent among patients with CHD compared to controls (p value<0.001), and were detected in approximately a quarter (33/144,22.9%) of fetuses with CHD, compared to only 1.5% (3/194) in controls (p value<0.001).[27] In 2016, this same research group reported a sensitivity of 27.3%, and a specificity of 88.6%, with positive and negative predictive values of 52.9% and 72.1%,respectively, of conventional fetal MRI, to identify persistent neonatal

brain abnormalities, indicating that fetuses with abnormal findings of fetal MRI and CHD images were more likely to have brain abnormalities on neonatal MR images (8 versus 1, p value=0.05).[28] These findings suggest that brain abnormalities, detected by MR images in utero, in fetuses with CHD are associated with an increased risk of postnatal preoperative brain injury. However, a substantial proportion of abnormalities on postnatal MR images were not present on fetal MR images.

Table1: Parameters evaluated and evaluation periods.

Author	Type Of Study	Population	Gestational age	Evaluated outcome	Outcome
E Hahn	CLINICTRIAL	133 new bornsor babies with a single ventricle • 11 subjects had aright ventricular hypoplasia lesion. • 122 subjects had left ventricular hypoplasia:103of them (84%) had HLHS.58of the subjects with HLHS (56%) had aortic atresia.	Four gestational periods: (1)20–23weeks (2)24–29weeks (3)30–33weeks (4) ≥ 34 weeks 14 ± 1 months of Birth (82 out of 133pts): BSID - II	1. Neurological development 2. Pulsatility index of the middle cerebral artery 3. Association Between fetal MCA-PI fetal and HC 4. Association Between fetal MCA-PI (middle cerebral Artery flow rate (MCA) pulsatility index (PI) a measure of resistance) and neurodevelopment 5. Association Between briometrics and neurodevelopment	**1**. For these 82 subjects, the mean MDI score was 88.5 ± 16 and the mean PDI score was 76.4 ± 19.8. These means were significantly lower than the population means of 100 ± 15 for these standardized tests(P<0.001). **2**. Of the 133 fetuses, 119 had sufficient Doppler traces for the MCA-PI calculation. There was a significant negative change in the Rate of change of the MCA-PI Z score from period 2 (24–29weeks) To period 4 (≥ 34 weeks) (−0.03 ± 0.28vs. - 0.26±0.34, P = 0.04) **3**. There was a significant negative change in the rate of change of the fetal Z HC score from period 2 (24–29 weeks) to period 4 (≥ 34 weeks) (0.11 ± 0.22 vs. - 0.07 ± 0.11, P = 0.03). **4**.The MCA-PI was independently and negatively associated with PDI **5**. There are not changes in EFW, FL or AC correlated with Neurodevelopment
Catherine Limpero-poulos	CASE-CONTROL	105 fetuses (50 CHD,55 controls) CASES: HLSH19 TGA13 OTHER: 18 CONTROLS: 55 Fetuses (healthy pregnant volunteers and pregnancies with anormal fetal echocardiogram due to family history of CHD or suspected CHD in the current pregnancy)	AG MRI:25 to 37 weeks (median, 30weeks)	**1.ICV**: It included CSF and brain, cerebellar, and brain-stem parenchymal volumes. **2.TBV**: Includes Brain cerebellar, And brainstem parenchymal volumes, but excludes intra ventricular and extra ventricular CSF volume **3. CSF**: Obtained by Subtracting TBV from ICV **4. Four metabolites By H-MRS: NAA,** choline, creatine and lactate.	**1 and 2**. Control fetuses: there were linear relationships between TBV and GA (R 2 = 0.98, P <0.001) and ICV and GA (R 2 = 0.96, P <0.001), with progressive increases in TBV and ICV during the third trimester. TBV and ICV were progressively smaller in CHD fetuses relative to Controls (P <0.001for both TBV and ICV). **3**.CSF volume in controls (R 2 =0.80, P <0.001) and the proportion Of ICV occupied by CSF volume (CSF: ICV; R 2 = 0.93, P <0.001) decreased with increasing GA. The CSF: ICV ratio, which normally decreases from ≈0.4 at 25 Weeks to ≈0.1 at term, was progressively higher in fetuses with CHD during the third trimester (P= 0.001) compared to controls. **4**.H-MRS spectra were successfully obtained in 75 fetuses: 36 with CHD (72%) and 39 controls (71%). The NAA: choline ratio Progressively increased during the third trimester in the controls, from≈0.1 at 25 weeks to≈0.8 at 36 weeks (R 2= 0.94, P <0.001) The NAA: choline ratio in CHD fetuses was significantly and Progressively lower with GA advancement (P <0.001) Independent predictors of the NAA: lower choline ratio included The diagnostic category (HLHS, TGA, pulmonary atresia, other CHDs Or control; P <0.001), absence of antegrade flow in the aortic arch (P= 0.01), and the presence lactate (P <0.001) Cerebral lactate was detected in 7 of 36 fetuses (20%) with CHD (5 With HLHS, 2 with TGA) between 29 and 35 weeks of GA. Overall, Fetuses with brain lactate had the lowest NAA adjusted for GA and TBV: choline. No control fetus had detectable brain lactate.

C. Clouchoux	CASE-CONTROL	48 fetuses (18 Cases with HLHS, 30 controls)	GA of 25.4 to 37.0weeks (mean GA for controls:30.5 ± 3.1weeksversus cases: 30.8 ± 3.8, P = 0.3). The GA median on MR was 30.14 (range:25.4–37.0).	1.Relationshipof Brain volumes of White and gray matter 2.Relationship Between blood flows and brain development in fetuses with HLHS 3.Sulcationpattern in fetuses with HLHS versus controls	**1**.Whiteand gray matter volumes were significantly lower in the HLHS group (P <0.001), with a difference that became Progressively greater after 30weeks of gestation. The difference in subcortical gray matter volume between the 2 groups was less pronounced, although statistically significant (P = 0.02). The lateral ventricular volume was not different between the 2 groups (P = 0.6). **2**.Low CPR (<1.0) was significantly associated with decreased White matter volumes (P = 0.02), sub cortical gray matter (P = 0.02), And lower surface area for the right hemisphere (P = 0.04). **3**.**1) The cingulate sulcus** was visible in controls from 25weeks GA, but not until 28 weeks GA in fetuses with HLHS; **2) the superior frontal sulcus** was visible from 27 weeks in control fetuses, but not until 30 weeks GA in HLHS fetuses; and **3) the anterior ascending branch** was visible at 32 to33 weeks GA in controls, but only at 36 weeks GA in HLHS fetuses.
Cynthia M Ortinau	COHORT	CASES: 19 fetuses Diagnosed with Moderate to Severe CHD. CONTROLS: 17 Fetuses of women with normal fetal echocardiogram.	Fetal MRI at mean ± SD of 26.3 ± 1.6 weeks for control fetuses compared to 26.9 ± 2.5 weeks for fetuses with CHD, ranging from 21.1 to 30.1weeksfor the entire cohort.	The SI of the surcal pattern, the area and depth of the sulcal basins and the relationships between them by each subject	Fetuses with CHD demonstrated altered global sulcal patterns in The left hemisphere compared to fetuses with TD (TD [SI,mean ± SD]: 0.822 ± 0.023, CHD: 0.795 ± 0.030, P = 0.002). There was no difference in cortical gyrification index, mean Curvature, or surface area.
N masoller	CASE-CONTROL	95 CASES WITH CHD -49Excluded (death and Termination of pregnancy) -The remaining 46 cases were born alive at term and survived the surgery. There were no differences in gestational age at delivery. CONTROLS: -The fetuses of the same gestational age with structural assessment of normal heart on second trimester ultrasound.	The GA median At the time of CHD diagnosis was 22 + 3 (range, 20 + 0 to 23+ 5) weeks.	1.Fetalbiometry: DBP, HC, AC and FL 2. Cerebral perfusion: MCA- PI, CPR and FMBV	1.Fetuses with CHD showed significantly lower MCA-PI and CPR Z Scores (−0.23 vs. 0.34 and−0.37 vs. 0.30, respectively P <0.001) as Higher Z scores for FMBV (2.35 vs. 0.15; P <0.001). FMBV> 95th percentile was observed in 81.1% of cases compared to 10.5% in controls(P<0.001) 2.The cases showed a significantly lower Z score of DBP and HC (- 1.61vs. 0.43 and0.89 vs. 0.09, respectively; both P <0.001) 3. Cases showed a higher proportion of BPD and HC measurements below the 5th percentile compared to controls (51.6% vs. 13.7%and26.3% vs. 4.2%, respectively; both P <0.001).

Ismee A	COHORT	CASES: 68 fetuses with CHD (N = 24 HLHS, N=21TGA, N=23TOF) -<26 weeks were enrolled after the fetal echocardiography. - 2 cases liminated by exclusion criteria (genetic alteration) **CONTROLS:** Normal controls with fetal echocardiography completed in order to ensure normal cardiac anatomy.	Serial biometric evaluations were collected three times during pregnancy: - At 18–26 weeks GA (F1), at 27–33 weeks GA(F2) and at 34–40 weeks GA(F3) - Subjects with CHD underwent Bayley Scales of Infant Development-IIIND tests at 18 months (provides three summary scores: Cognitive, Language, and Motor. Theses cores have a population mean and standard deviation of 100 ± 15)	1.Differences in fetal growth rates between fetuses with and without CHD: Parameters: DBP, HC, AC, FL and EFW 2.Associations between fetal growth and neuro developmental out come in early childhood	1. Fetuses with CHD show lower growth rates compared to controls, most notably for HC. -In F1, 18–26 weeks, CHD fetuses demonstrated smaller biometric percentiles compared to controls. In F2, 27–33 weeks, AC was statistically lower among the CHD group. In F3, 34-40 weeks the percentiles, BPD, HC, AC and EFW were smaller among the CHD group. -There were no significant differences in the HC / AC ratio between the groups in any period of gestational age. -The differences between the groups were only observed for HC inF2 (1.5 vs. 0%, P = 0.04) and F3 (14.7 vs. 0%, P = 0.01) and FL in F3 (10.2 vs. 0%, P = 0.04). 2.Fetalbiometryvariablesthatwerecorrelated-withcognitivescoreincluded -AC in F1 (r = 0.32, P = 0.049), HC / AC in F1 (r = −0.39, P = 0.02) And average HC /AC (r = −0.4,P = 0.007). -Language score was significantly correlated with FL/ BPD in F2 (r =0.32, P = 0.037) and the mean of HC/ AC (r = −0.3, P = 0.045). -The motor score was not correlated with any biometric variable.
Schellen C	CASE-CONTROL	CASES: 30 fetuses with confirmed TOF It was retrospectively studied fetal MRI data that was acuired betweenMarch2004 and April2014. - 6 excluded due to chromosomal alteration and excessive fetal motion image artifacts. **CONTROLS:** 28 normal control fetuses with normal fetale chocardiography.4 excluded due to excessive fetal movement during image acquisition. FINAL: 24 fetuses with TOF and 24normal control fetuses were included in the final cohort study(n=48)	The GA meanwas179.7±25.3 days (n = 24), with a median age of 176 days (25 + 1 GW) among fetuses with TOF and179.3 ± 24.9 days (n = 24), with a median of175days old (25 + 0 GW) in the control group. Control cases and fetuses were matched according to GA, and 24 matched pairs were obtained with a GA difference of no> 4 days between matched subjects and an average difference of 1.00± 1.02 days.	Early changes in: - TBV - GMV - SBV	TBV was significantly lower (P <.001) in early (<25 GA) and late TOF cases. Both GMV (P = .003) and SBV (P = .001) were affected. The GMV to SBV ratio decreased in fetuses with TOF (P = .026). Compared to normal fetuses, ventricular volume increased (P=.0048). The external cerebrospinal fluid was enlarged in relation to the size of the head (P <.001). Intracranial cavity volume (P= .314) and cerebellar volume (P = .074) were not significantly reduced in fetuses with TOF

Masoller	COHORT	**CASES:58** patients The CHD sub group 1 was defined as the cerebral perfusion with well or moderately preserved placental blood content and included septal defects, right heart defects, truncated conical defects other than transposition of the great vessels, and complex CHD. The CHD subgroup 2 (low-placental blood brain perfusion) included severe obstruction of the left outflow tract with reverse flow in the aortic isthmus or trans position of the great vessels. **CONTROLS: 58** **patients** Normal ultrasound control	Fetal ultrasound mid-pregnancy at 20-24 weeks of gestation, full-term fetal brain MRI at 36-38 weeks of gestation	1. Biometry and Doppler: HC, DBP, AC, and FL, and Brain Perfusion by MCA-PI, CPR, and FMBV 2. Resonance Report: Predictors of abnormal brain development evaluated by MRI at term 3. Perinatal outcomes	1. Fetuses with CHD had significantly lower mean Z scores of DBP and HC, and a higher proportion of fetuses with DBP and HC <5percentile. No differences were observed in HC and FL. The fetuses with CHD showed significantly lower mean Z scores for MCA-PI and CPR and a significantly higher mean Z score for FMBV compared to controls. 2. Resonance Results: CHD fetuses showed significantly smaller brain, intracranial, and opercular volumes than controls. The results of the step-by-step logistic regression showed that fetal MCA-PI (OR,12.7; P= 0.01), CPR (OR,8.7; P=0.02) and fetal HC (OR, 6.2; P = 0.02) in half of pregnancy were independent predictors of abnormal brain development. The other variables analyzed, including the BPD, FMBV and CHD subgroup, were not identified as statistically significant independent predictors by the model. Cortical sulcation: fetuses with CHD had significantly decreased depths for left and right parietooccipital, cingulate, and calcarine fissures compared to controls. 3. Perinatal Outcomes: There was a non-significant trend for lower birth weight in CHD cases, due to a higher proportion of babies born small for gestational age compared to controls (17% vs. 2%, respectively; P <0.01). Newborns with CHD had significantly lower CH at birth than controls (335mm vs. 349mm; P <0.01).
Alina Weissmann-Brenner MD	CASE-CONTROL	**CASES:** **46** fetuses diagnosed with CHD under went to brain MRI. The CHD was classified according to site abnormalities, 4-chamber view (4CV), outflow tracts, arches and veins, as well as cyanotic or complex CHD. **CONTROLS**: 113 healthy brain MRI	There is no parameter of gestational age	The correlation between CHD and brain injury using fetal brain MRI. MRI results of different CHD types	Fetus with CHD: Findings on MRI of the brain suggest pathogenesis in the womb of neurological and cognitive abnormalities found during infant development No significant differences in brain pathologies were found between the different CHD classifications. Compared to the control group, significant differences were founding general brain pathology in cortex abnormalities and in additional axial findings in the study group. Significantly higher rates of general brain pathologies, ventricular pathologies, cortex pathologies, and biometric parameters were found in the cyanotic group compared to the complex group and the control group.

Masoller N	COHORT	58 CHD / 58 controls in whom Doppler ultrasound and FBMRI was performed. It was divided into 2 CHD groups: • **Class A:** There is BO involvement as in the cases of pathologies with obstruction of the left outflow tract with reverse flow in the aortic isthmus (HLHS (n = 1), severe AS (n =5) or HAA (n = 13)) and TGA (n =10). • Class B: Without BO involvement (SD (n = 3), TOF (n =9), CAT (n = 1), TA(n=4), AE(n=5), severe stenosis or pulmonary atresia (n = 5), CHD (n =2).	Weeks 36-38	**1.Ultrasound** -HC -FPD **2.FBMRI** -BV -CD -Metabolism	**1**. HC: CHD class A and B had a CC <Controls (Class A: 327± 13 Class B: 338 ± 14 Controls: 349 ± 11) (p <0.01). BPD <p5 (Class A:59, Class B:28 Controls :3) (p<0.01) and the Z score (Class A: −1.76 ±0.64, Class B: −1.25 ± 0.75 Controls:0.21 ± 0.97) (p <0.01) was lower vs controls. CC <p5 (Class A: 41, Class B: 21 Controls: 3) (p <0.01) and the Z score (Class A: −0.99 ± 1.07, Class B: −0.39 ± 0.10 Controls: −0.03 ±047) (p<0.01) was lower vs controls. FPD: CHD class A and B had PI MCA <p5 (Class A: 38, Class B: 17Controls:0) (p<0.01) z score (Class A:−0.95±0.95,ClassB:−0.29± 1.14 Controls: 0.18 ± 1.06) (p <0.01) and the BPR significantly lower vs controls (Class A: 35, Class B: 14 Controls: 0) z score (Class A: −0.87 ± 1.10, Class B: −0.26 ± 1.00 Controls: 0.05 ± 1.01) (p <0.01) FBP> CHD vs controls; p> 95 (Class A: 86, Class B: 59 Controls: 7) z score (Class A: 2.30 ± 0.80, Class B: 1.57 ± 0.93 Controls: 0.27 ± 1.12) (p<0.01) **2**. BV: CHD<vs controls (p<0.01)o TBV (Class A: 306.7 ± 21.9, Class B: 329.7 ± 32.3 Controls: 344.4 ± 22.0) (p<0.01)o TBV (Class A: 382.2 ± 22.1, Class B: 406.2 ± 40.0, Controls: 514.1 ±36.1) (p <0.01)o LOV (Class A: 3.33 ± 0.62, Class B: 3.62 ± 0.57 Controls: 5.79 ± 1.27), LOV (Class A: 33.20 ± 0.77, Class B: 3.59 ± 0.60 Controls: 5.55 ± 1.59), and total (Class A : 6.53 ± 1.24, Class B: 7.20 ± 1.03 Controls:11.33 ± 2.65)(p <0.01) CD:CHD have significantly decreased depths: LPOF, RPOF, CPOF And ca POF, POFLIL vs controls (p<0.01). **Metabolism:** CHD (FL and BG)> Inositol / Choline and <N-acetyl aspartate/ Cho and Cho/Creatinevs controls(p <0.01).CHD have significant changes in CD, more pronounced in CHD with severe OC reduction.
H Olshaker	COHORT	46 CHD (male: 19, female: 27) compared with normality chart. • HLHS (n=4) AS(n=1) CA(n=3) IAA (n=2) MS(n=2) TOF (n=3) PVA (n=2) PS(n=2) TA (n=1) EA(n=1) TR(n=8) TGA (n=11) VSD(n=16) ASD (n=6) PAF(n=6) • Fetuses with > 1CHD (n=24)	Weeks 32-34	**VC** 1) SBV 2) RHV 3) LHV 4) CV 5) CV/CBVS ratio	**1)** SBV showed no difference between groups. **2 and 3)** RHV and LHV showed no difference between groups. **4)** The mean CV (22.64+/- 29.8) was CHD <vs controls (p <0.05) **5)** CV/CBVS ratio (19.55 +/- 27.66) was CHD <vs controls (p<0.05)

C Limpero-poulos	OBSERVA-TIONAL	103 CHD (Male: 61-Female:42) • TGA (n=31)30% HLHS (n=20) 19% DOTRH (n=13) 13% TOF (n=11)11% AVC (n=8) TA(n=8) VSD(n=4) PA (n=3) EA(n=2) PS(n=2) AS (n=1) CA (n=1) CAT (n=1)	•FBMRI: Ges-tational mean 32.71 ±3.61 weeks (median, 33.71weeks; range,23.86-38.57weeks) • PMRI: Average of 6.8 ± 12.2 days (median, 3 days; range, 0-76 days)	1. FBMRI 2. PRMI	1. The RR of presenting abnormal PMRI findings after FBMRI was1.90 (95% CI 1.08-3.33; P = .03). This translated into Sen: 27.3%, S:88.6%, PPV: 52.9%, and NPV: 72.1% to detect brain abnormality from an FBMRI. • Fetuses with abnormal findings on FBRMI and cyanotic CHD were significantly more likely to have brain abnormalities on PMRI (8versus 1, p = 0.05). 2. Newly acquired brain injuries were significantly more frequent in neonates with single-ventricular CHD (15 versus 5; P = .002) and in those who underwent cardiac catheterization before PMRI (P =.006).
Cynthia M	COHORT	16 CHD • HLHS • TGA • PA • TOF • DOTRH • CAT • SV 15 healthy fetuses	32weeks o FBMRI (week32), pre-surgical, post-surgical and PMRI were takenat3 months GA.	**1. TBV** **2. CGMV** **3. WMV** **4. SGMV** **5. CV** **6. CF**	1. The increase in TBV (FBMRI) up to that of 3 months postnatal was 11.5 cm3 x week in CHD vs. 16.7 cm3 x week in controls (p =0.0002). There is an association between GA in FBMRI and TBC, where TBV increased with GA (p <0.0001) There were no group differences in TBV on FBMRI, but infants with CHD had a TBV <preoperative (p <0.001) and 3-month PMRI (p =0.0001). 2. Brain growth followed a similar path for CGMV (p <0.0001), SGMV (p = 0.002) and VC er (p = 0.005). 3. There was no difference in the growth of TBV (4.4 cm3 versus5.3 cm3, p = 0.30) Brain injury was associated with <TBV on the 3-month PMRI (p =0.02). 4. Infants with CHD had <SGMV (0.8 cm3 versus 1.1 cm3, p =0.002) 5. Infants with CHD had <CV (1.4 cm3 versus 1.8 cm3, p= 0.005). 6. There was no difference in the CF (4.5 cm3 versus 3.0 cm3, p =0.085).
C Limpero-poul	OBSERVA-TIONAL	338 fetuses: Male: 182 (53.8%)/Female:156 (46,2%) (FBMRI) o144 CHD (Male:82/ Female:62) • HLHS (n=32)22.2%TGA (n=27) 18.8%DOTRH (n=16)11.1%TOF (n=17)11.8% PA (n=12) 8.3%AVC(n=7) EA (n=6) TA (n=6) VSD(n=4)) PE (n=2) CAT (n=2) CA(n=1) o194healthy (Male: 100/Fe-male:94)	•30.61 +/- 4.67 weeks, fetuses with CHD • 29.94 +/- 5.14 weeks, healthy fetuses	1. IV 2. IES 3. WMC 4. CVH 5. White matter signal hyperintensity on T2 NMR 6. Normal	1. IV was more frequent in fetuses with HLHS (5/12, 41.7%), while STI was more common in fetuses with DOTRH (3/10, 30.0%). 2. IES was exclusively reported in fetuses with CHD and was present in 10 cases (9 in the third trimester), making this the second most common abnormality. 3. Abnormalities in white matter signal, cysts, and vermian hypoplasia were reported exclusively in the subgroup with cyanotic lesions. 4. Of the 3 fetuses with isolated lower vermian hypoplasia, the first had HLHS, the second was diagnosed with TOF, and the third had CAT. 5. Immature brain appearance was reported in 3 fetuses, one with TOF, the second with DOTRH, and the third with TGA. 6. Brain abnormalities detected on FBMRI images were more frequent in CHD (P <0.001) and were detected in approximately aquarter (33/144,22.9%) of fetuses with CHD vs.1.5% in controls (P<0.001).

Liqun Sun	CASE-CONTROL	• 30 CHD (FBMRI)o Univentricular (n=8) o Double ventricular (n=22):TGA (n=7)/ TOF(n=7) • 30 healthy	• 36weeks o FBMRI in T2 sequence and contrast mapping.	**1. BV** **2. SaO2 and FBF in the main vessels of the FC**	1. BV was correlated with SaO2 in AA and CFBO (r = 0.37 p =0.004). There was no difference in FBF and O2 extraction by the brain vs controls (p = 0.5), however there was a mean reduction of 32% in CFBO with CHD (p <0.001). This was associated with a 13% mean reduction in BV (p <0.001) The BV CHD <vs controls except in TGA and single ventricle (p =0.0001) 2. In CHD, a reduction in OCUV (p <0.001) and a failure in the transport of O2 from the placenta to AA was evidenced with a decrease in SaO2 of 10% (p <0.001). We found a mean reduction of 6% in OCUV (p = 0.0004), which was associated with a mean reduction of 17% in O2 delivery to the FC. In normal controls, the mean SaO2 of the AA was 7% higher than in the PAT, while in fetuses with CHD the mean SaO2 of the AA was only 2% higher than the SaO2 in the PAT, of Thus, transmission was responsible for a significant increase in AA SaO2 vs. SaO2 in PT in controls but not in fetuses with CHD (p = 0.03). There was a 30% reduction in VOC in univentricular vs. biventricular fetuses with CHD (p = 0.003), and this was associated with a 20% reduction in e OCUV (p = 0.002). The combination of a SaO2 and a lower FBF in the UV in fetuses with CHD resulted in a 17% reduction in oxygen delivery to the CF (p = 0.006), which was associated with a 17% reduction in the CFBO (p = 0.007). Delivery of oxygen to the HR was further reduced in the univentricular fetuses vs. biventricular fetuses (p = .0.03) and the univentricular fetuses also had lower SaO2 AA, although SaO AA was significantly lower than controls for all CHD subgroups except TGA (p = 0.0001) Cerebral oxygen delivery was lower in all CHD subgroups vs controls except in univentricular CHD (p = 0.0001).
Elisabeth Mlczoch	OBSERVATIONAL	• 53 CHD (RCF)o **Groupe1:** Right outflow obstruction if the pulmonary artery was smaller than the aorta (PS, TOF, PA, or TA) (n = 18) •Univentricular (n=4) •Biventricular (n=14):TGA(n=3) /Normal arteries (n=11)o Groupe 2: Left out flow obstruction if the aorta was smaller than the pulmonary artery (AS, CA, HLHS) (n = 10) • Univentricular (n=3) • Biventricular(n=7): TGA (n=1) /Normal arteries(n=6)o Grupo 3: Miscellaneous if both arteries were the same size (DS and complex coronary heart disease) (n = 25) • Univentricular (n=3) • Biventricular (n=22): TGA(n=4) / Normal arteries (n=18	20-38weeks (Average: 28week) • **Prenatalechocardiogram**:16-32 weeks (average: 24weeks). • FBMRI: 4weeks after taking theechocardiogram20-37 weeks (average: 28weeks)	1.**Malformations** (HP, CCA, CH, ICD) 2. **Acquired** (IV, VH,GC, ISS) 3.**Changesin CF** (ACy, CM) 4.Normal	1. Malformations represented 33% of brain anomalies. 2. Acquired lesions represented 24% of brain abnormalities. 3. CF space width abnormalities represented 43% of brain abnormalities 4. Fetal MRIs in the study cohort yielded normal results in 32fetuses and a brain abnormality in 21 fetuses. Thus, congenital brain disease was found in 39% of the CHD study fetus cohort

Clinictrial (n=1)

Hahn E[29] investigated the association of fetal growth and cerebrovascular resistance at different periods of gestation, monitoring the ND at 14 months by means of the evaluation with the mental development index (MDI), which assesses cognitive ability and the averages core of the psychomotor development index (PDI), in patients with univentricular heart disease.[29] This study pointed to the third trimester as a crucial time for fetal somatic growth and neurological development. It was found that as the gestation progressed the MCA-PI decreased more than would be expected for GA, which shows a decrease in cerebro vascular resistance. In addition, there was a decreased growth in fetal HC later in gestation and MCA-PI was independently and negatively associated with the psychomotor development index. When evaluating the 82 subjects included in the sample, it was found that the DMI scores were significantly lower than the population means for these standardized tests (p value<0.001). No changes were found in the EFW, FL or AC correlated with the ND.

Risk of bias assessment Case-control studies

In general, the 6 case-control studies found are intermediate or high risk due to the lack of management of confounding factors and the ways in which the outcome is measured in both cases and controls (Table 2).

Cohort studies

All 9 included cohort studies were at intermediate risk of bias as confounding factors are similarly not managed appropriately (Table 3).

Clinic trials

The only included clinical trial[29] was at high risk of bias, because the authors do not present methods of randomization or concealment of the evidence used (Table 4).

Table 2: Case-control risk of bias assessment.

Questions	Limperopoulos C	Clouchoux C	N Masoller	Schellen C	Weissmann Brenner A	L Sun
Were the groups comparable between each other?	Yes	Yes	Yes	Yes	Yes	Yes
Were the case sand Controls matched?	No	Not clear	Not clear	Not clear	No	No
Were inclusion and exclusion criteria the same for cases and controls?	Yes	Yes	Yes	Yes	Yes	Not clear
Was the exposure measured in a standard and valid way?	Not clear	Yes	Not clear	Yes	Yes	Yes
Were the confounding factors identified?	No	No	No	No	Yes	No
Strategies to deal with the confounder?	No	No	No	No	No	No
Was the out come measured in a standard and valid way?	Not clear	Yes	Not clear	Yes	Yes	Yes
Was the period of Exposure sufficient?	Yes	Yes	Yes	Yes	Yes	Not clear
Was the statistical analysis appropriate?	Yes	Yes	Yes	Yes	Yes	Yes

Table 3: Assessment of risk of bias in cohort study.

Study	Similar groups?	Exposure measured in similar ways?	Exposure measured in a reliable way?	Confounding factors?	Strategies to avoid the confounder?	Free from the outcome at the start of the study?	Out comes measured in reliable way?	Time of monitoring reliable?	Few losses in them monitoring?	Strategies evaluating the losses?	Adequate statistical analysis?
Cynthia M	Yes	Yes	Not clear	No	No	Yes	Not clear	Yes	No	No	Yes
Ismee A	Yes	Not clear	Yes	No	No	Yes	Yes	Not clear	Yes	No	Yes
Masoller	Yes	Yes	Not clear	Not clear	Not clear	Yes	Yes	Yes	No	No	Yes
Narcís M	Yes	Not clear	Yes	Not clear	Not clear	Yes	Yes	Yes	Yes	No	Yes
H Olshaker	Yes	Not clear	Yes	Not clear	Not clear	Yes	Not clear	Not clear	Yes	No	Yes
M Brossad-Racine	Yes	Yes	Yes	No	No	Yes	Not clear	Not clear	Yes	No	Yes
Cynthia M	Not clear	Yes	Not clear	No	No	Yes	Yes	Yes	Yes	No	Yes
M Borssard-Racine	Yes	Yes	Yes	Not clear	Not clear	Yes	Yes	Yes	Yes	No	Yes
Mlczoch	Not Clear	Not clear	Yes	Not clear	Not clear	Yes	Yes	Yes	Yes	No	Yes

Table 4: Clinical trial risk of bias Assessment.

Study	Randomization	Concealment	Blinding of the patients	Blinding of the evaluators	Losses in The monitoring	Selective reporting	Others
E Hahn	Risk not clear	High risk	High risk	High risk	Low risk	Low risk	Not clear

Discussion

CHDs represent an important cause of ND alterations in childhood.[1-5] Khalil et a described brain disorders diagnosed in fetal neuro imaging for all CHDs, with a prevalence of 34% for TGA and 49% for HLHS.[3,9,10] Investigations focused on the alterations in perioperative corrective surgery and cardiopulmonary bypass, however more than half of the children had cognitive and structural deficiencies prior to the surgical procedure, which is why it was raised, with more evidence, that the alterations of the CNS occur since intrauterine life.[9,11,12] For all types of CHD a decrease in fetal growth was found, mainly in HC, BPD (Z-score-percentile<5) and CC/AC ratio.[22] Morphological findings were associated with decreased cognitive and language development scores in childhood in fetuses between 18-26 weeks of GA. The aforementioned evidences that apart from the oxygenation that CHD presents from the postnatal point of view (cyanotic and non-cyanotic) the morphological alterations lead to a functional alteration that is evidenced in postnatal tests. Growth alterations of the cephalic diameters mentioned would evident when noxa occurs early in gestation as a result of CHD.[29,7,23,24] It is important to highlight that our findings are complemented by the results found in the literature where up to 59% of newborns with TGA and HLHS (Figure 1), have a delay in brain growth in the third trimester.[3] It is striking how Williams[22] although they report alterations in fetal biometric measurements, they do not show a direct association with an alteration in ND in childhood.[22,29,23] The only clinical trial published in this regard,[29] showed a postnatal alteration, in the cognitive capacity and psychomotor development of newborns with univentricular CHD after follow-up for 14 months.[29] Patients with ventricular hypoplasia will have cognitive impairment during postnatal monitoring. Several authors have evaluated brain and cerebrospinal fluid volumes as an alteration of the CNS secondary to a decrease in cerebral perfusion.[6,21] Decreased brain volumes have been shown in fetuses affected with CHD, much more evident in fetuses with HLHS and TOF, in which an alteration in brain volumetry predominantly seen in TBV is found, ICV, white-matter-volume, and cerebellar-volume.[6,13,21] They do not report significant differences in the volumes of cortical/subcortical or ventricular gray matter.[21,23-25] The above findings are striking since the measurements of brain volumes are reproducible measurements on MRI by specialists in reading fetal imaging studies. Donofrio[11] established the difference between brain abnormalities due to hypoxic-ischemic

lesions vs. acquired-malformations.[11] Severe structural injuries, such as holoprosencephaly, were not excluded resulting in an overvaluation of findings, with an association of 39% congenital brain disease in fetuses with CHD.[10] By not excluding CNS pathology, it is very difficult to determine if the origin of the lesion could have been in CHD, therefore, it is evident howpreviousstudiessuggestthatcerebralmorphologicalevaluationrequirestodeterminewhichlesions are secondary to CHD oxygenation disorders.

Ortinau[4] conducted a study in which they compared cortical development by describing the normal surcal pattern with the finding that fetuses with CHD had altered surcal patterns predominantly in the left hemisphere (p value=0.002). These differences are represented by alteration from the early formation of the grooves and in the position of their precursors (p value=0.006) as well as the inter surcal relationships (p=0.033).[4] In our review, it was found three studies that evaluated the surcal pattern with similar findings. The greatest involvement remains persistent in fetuses with univentricular CHD, where the cingulate sulcus is not visible at the 28 weeks of GA and the superior frontal sulcus is not visible at the 30 weeks, opposite in healthy fetuses.[13] Furrow patterns were predominantly altered in the left hemisphere with significantly decreased depths for parieto-occipital, cingulate, and calcarine fissures.[4,23,24]

The most studied parameter of cerebral perfusion by means of Doppler is the alteration of the ACM-IP and the CPR. This alteration appears in fetuses with HLHS, AS or AAH, represented as a decrease in PI beyond that expected for GA.[29] The above implies a compensatory mechanism of cerebral vasodilation as a consequence of inadequate perfusion due to an alteration in cardiac structurality, the alteration in univentricular vs. biventricular CHDs being more representative and being an independent factor of abnormal brain development.[7,23,24] This finding, although it seems highly related to central hypo perfusion secondary to CHD, appears frequently in fetuses with IUGR who present al eft ventricular dysfunction that alters the PSV-MCA without presenting an alteration in blood viscosity. This hemodynamic finding could be increased in fetuses with both abnormalities CHD/IUGR. If the fetus with CHD also presents IUGR, its prenatal neurological prognosis would be deleterious in the ND.[3,4] Alterations such as periventricular leukomalacia, cerebralatrophy and white-matter damage, evidenced both prenatally and postnatally, were findings in which most of the authors agree (Figure 1).[3] Regarding the evaluation and comparison of prenatal MRI studies compared to postnatal findings, one study evaluated prenatal vs. postnatal performance with a finding of sensitivity 27.3%, specificity 88.6%, PPV52.9%, and NPV of 72.1% to detect brain abnormalities priortobirth.[28] Likewise, the values for prenatal NS in terms of sensitivity, specificity, NPV and PPV are 96%, 87%, 93% and 93% respectively.[30,31] Not all disorders are identified prenatally, which could be a consequence of technical/observer limitations.

This systematic review has brought together the most relevant studies regarding the important effect of hypoxia in utero secondary to CHD evident in prenatal examinations. Our findings suggest that in the included literature it is evident how the lesions occur in a prenatal stage and are corroborated at birth, demonstrating how cardiac surgery was not the cause of said lesions but CHD per se, however cardiac surgery could present alterations in the cerebral circulation with consequences. Fetuses with isolated CHD present structural neurological alterations since intrauterine life, even from early stages of fetal development, evidenced by NS and fetal-MRI. This highlights the importance of studying the CNS of fetuses with CHD and the relationship between structural brain alterations and ND impairment since prenatal stages. Long-term prospective multicenter cohort studies are required, with prenatal and postnatal evaluation that allows evaluating the impact of these structural alterations on the incidence of cognitive development disorders.

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Conflict of Interest

Authors declare that there is no conflict of interest.

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Annex1

exp White Matter/White Matter.tw (White adj3 Matter).tw

(occipitofrontal circumference).tw (cephalic circumference).tw

Exp Brain Diseases/Brain.tw (Intracranial adj3 Disorders).tw (Intracranial Disorder).tw (Encephal* Diseases).tw (Encephal* adj3 Diseases).tw Encephal*.tw

exp Central Nervous System/"Central NervousSystem".tw Cerebrospinal Axi.tw (Cerebrospinal adj3 Axi).tw exp Brain/ exp Magnetic Resonance Spectroscopy/Magnetic Resonance.tw (Magnetic adj3 Resonance).tw MRSpectroscopy.tw (MR adj3 Spectroscop*).tw (NMR adj3 Spectroscop*).tw NMR Spectroscop*.tw

exp Heart Diseases/(Heart Disease).tw (Heart adj3 Disease).tw (Cardiac Disease).tw

Cardiac adj3 Disease).twcardiopathy.tw exp Fetus/Fetus.twFetal.tw