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Review Article

Congenital Heart Defects and Measures of Prenatal Brain Growth: A Systematic Review

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ABSTRACT

BACKGROUND: We summarize the evidence for an association between congenital heart defects and prenatal brain growth through a systematic literature review. Congenital heart defects are among the most common malformations, affecting approximately six per 1000 live births. The association between congenital heart defects and long-term neurodevelopmental disorders is well established. Increasing evidence suggests an association between impaired prenatal brain growth and neurodevelopmental disorders in children with congenital heart defects. **METHODS:** Systematic literature searches were performed in PubMed and EMBASE. We included original studies comparing fetuses or newborns with congenital heart defects to reference fetuses or newborns with respect to brain biometrics, including biparietal diameter, brain volume, and head circumference at birth. The study characteristics and the results were extracted and presented in tables. No meta-analysis was undertaken. **RESULTS:** Twenty-eight studies were included. All except two studies found an association between congenital heart defects and measures of reduced prenatal brain growth. The strongest evidence concerned hypoplastic left heart syndrome, tetralogy of Fallot, and transposition of the great arteries. **CONCLUSIONS:** The literature suggests an association between congenital heart defects and measures of impaired prenatal brain growth. However, most studies were small and failed to include important potential confounding factors and to address other sources of potential bias as well. Future large-scale studies that address potential confounders are warranted.

Keywords: congenital heart disease, fetal growth, brain, cerebral, neurodevelopment, pregnancy

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Introduction

Congenital heart defects (CHDs) are among the most common congenital malformations. Moderate to severe defects are present in approximately six per 1000 liveborn infants,[1] and the association between CHD, low birth weight, and fetal growth restriction is well established.[2-4] Although prenatal diagnosis and surgical interventions have led to substantial improvements of long-term survival, CHD remains a leading cause of serious morbidity and mortality in childhood.[5] The most common and distressful long-term complications are neurodevelopmental disorders, including disorders of motor function and verbal skills, as well as social and academic skills. These disorders have a major impact on the quality of life of the patients and economic

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consequences for society as a whole.[6,7] Recently this has been emphasized in a statement by the American Heart Association calling for an increased focus on the evaluation and management of neurodevelopmental disorders in children with CHD.[7]

In recent years, prenatal and preoperative factors have been recognized as important causes of neurodevelopmental disorders.[4,8-13] The organogenesis of the heart and the brain starts during the first trimester. However, brain development and growth continues through the subsequent trimesters and during the postnatal period,[14,15] and the timing and mechanisms of abnormal brain development *in utero* is currently a subject of increasing interest.[16-18]

Although the causes of impaired neurodevelopment remain widely unknown, both continuous measures of small brain biometrics (e.g., HC [head circumference] in centimeters or HC *z* scores)[9,11,19] and microcephaly (e.g., using a cutoff at HC < -2 SD)[20] prenatally or at birth have consistently been shown to be associated with neurological and neurobehavioral abnormalities during childhood. Conversely, but in accordance with the findings in the general population,[21,22] a smaller HC to abdominal circumference (AC) ratio, a measure of proportionality of the fetus or the newborn, has recently been associated with improved measures of cognition and language development.[23]

The aim of this systematic review was to examine the association between CHDs and measures of prenatal brain growth and to evaluate methodological issues important for the interpretation of the findings as well.

Methods

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement including the 'population, interventions/exposures, comparators, outcomes, and study design' (PICOS) approach.[24]

Search strategy

Most of the included articles were identified by systematic searches in PubMed and EMBASE on March 21, 2016. "MeSH" (PubMed) and "Emtree" (EMBASE) terms as well as free text searches included the relevant terminologies with combinations of CHDs and measures of fetal brain growth (see the exact search strings in the Supplemental Material). No language, time period restrictions, or other filters were applied. Two authors (T.H. and N.B.M.) extracted results from the systematic searches.

First, the titles were screened and duplicates were excluded. Second, conference abstracts and editorials were excluded before the full evaluation of first the abstracts and then the full articles. Third, reviews, articles with completely overlapping datasets, and articles including no measures of brain growth were excluded. Finally, references and citations of the included articles were searched using the Scopus database to identify relevant articles not identified by the systematic literature searches. These articles underwent full evaluation before inclusion.

Study selection criteria

The study selection criteria were based on the 'population, interventions/exposures, comparators, outcomes, and study design' approach.[24] The studied populations were fetuses or newborns. The intervention/exposure under study was CHDs. This review included studies comparing fetuses or newborns with CHD to reference fetuses or newborns without CHD or to external reference populations. Fetal or neonatal brain biometrics including HC, biparietal diameter (BPD), and brain volume were considered the outcomes. The previous literature has shown a high correlation between these measurements.[25-28] The outcomes were assessed by physical examination, ultrasound, or magnetic resonance imaging (MRI; including volumetric MRI). Both studies reporting longitudinal changes in biometrics over time (actual fetal growth) and studies reporting cross-sectional measures (proxies of fetal growth) were included. We considered measures of brain "maturity" measured by biochemical markers or brain structure to be different outcomes and did not include these outcome measures. Eligible study designs included cohort studies, cross-sectional studies, and case-control studies. Editorials, comments, reviews, meta-analyses, and case series as well as case reports were excluded.

Results

Study selection

A total of 3952 records were identified in the database searches. After screening of the titles and the abstracts, 50 records were assessed for eligibility and reviews, articles with identical datasets, and articles not including the relevant outcomes were excluded. After a Scopus search of references and citations of the eligible articles, three additional articles were added to the 25 eligible articles. Thus a total of 28 studies were included in the systematic review (see Figure).

Of the 28 studies, Hangge et al.[15] evidently included some of the same individuals who had been studied earlier by Hinton et al.,[14] but the later study population was larger because data were collected over a longer interval. Masoller and colleagues' 2016 study included an overlapping but smaller study population than their own earlier analysis because several subjects either did not survive to term, were excluded during pregnancy, or their families declined the examination by MRI.[29,30] Their later study, however, provided additional data on brain volume.[29] Clouchoux et al.[31] studied a subgroup of individuals who had been studied by Limperopoulos et al.,[16] but Clouchoux et al. included observations at more different time points. Consequently, the datasets were not considered identical and all six studies were included in the review.

Characteristics of the included studies

CHD was identified either prenatally (11 studies) or postnatally (17 studies). The outcomes were assessed prenatally (11 studies), postnatally (14 studies), or both prenatally and postnatally (three studies). Eight studies investigated continuous absolute HC (in centimeters). Other HC-related outcomes included HC *z* score for gestational age (nine studies), HC percentile for gestational age (four studies), adjusted HC mean difference (one study), HC/weight ratio (two studies), and HC/AC ratio (one study). Two studies investigated continuous BPD (in centimeters). Other BPD-related outcomes were BPD *z* scores for gestational age (four studies) and BPD percentile for gestational age (one study). Seven studies reported measurements of brain volume.

The studies assessed outcomes gathered from ultrasound data (ten studies), medical records (11 studies), physical examination (five studies), MRI (seven studies), or by a combination of these methods.