Prevalence of Prenatal Brain Abnormalities in Fetuses with Congenital Heart Disease: Systematic Review

Asma Khalil*, Sarah Bennet*, Basky Thilaganathan*, Dario Paladini†, Paul Griffiths‡, Julene S Carvalho*§

*Fetal Medicine Unit, St. George's University of London, London, UK

† Fetal Medicine & Surgery Unit – Istituto G.Gaslini, Genoa, Italy

‡ Academic Unit of Radiology, University of Sheffield, Sheffield, UK.

§ Brompton Centre for Fetal Cardiology, Royal Brompton Hospital, London, UK

Corresponding author:

Dr Asma Khalil

Fetal Medicine Unit

St George's University of London

Cranmer Terrace,

London SW17 0RE

Telephone: +442032998256

Fax: +442077339534

E-mail: asmakhalil79@googlemail.com

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/uog.15923

ABSTRACT

Objectives: Studies have demonstrated an association between congenital heart defects (CHD) and postnatal brain abnormalities and neurodevelopmental delay. Recent evidence suggests that some of these brain abnormalities are present even before birth. The primary aim of this study was to perform a systematic review to quantify the prevalence of prenatal brain abnormalities in fetuses with CHD.

Methods: MEDLINE, EMBASE and The Cochrane Library were searched. Reference lists within each article were hand-searched for additional reports. The outcomes included structural brain abnormalities (MRI), changes in brain volume (MRI, 3-D volumetric MRI, 3-D ultrasound and Phase Contrast Magnetic Resonance), metabolism or maturation (Magnetic Resonance Spectroscopy and Phase Contrast Magnetic Resonance) and blood flow (Doppler ultrasound, Phase Contrast Magnetic Resonance and 3D Power Doppler ultrasound) in fetuses with CHD. Cohort and case–control studies were included. Cases of chromosomal or genetic abnormalities, case reports and editorials were excluded. Proportion meta-analysis was used for analysis. Between-study heterogeneity was assessed using the I^2 test (Registration number: CRD42015025546).

Results The search yielded 1,943 citations; and 20 studies were included in the review (n=1175 cases, 221 in the meta-analysis). Three studies reported data on structural brain abnormalities, while data on altered brain volume, metabolism and blood flow were reported in 7, 3 and 14 studies, respectively. The three studies reporting data on structural brain abnormalities were suitable for inclusion in a meta-analysis (221 cases). The prevalence of prenatal structural brain abnormalities in fetuses with CHD was 28% (95% CI 18%–40%), similar prevalence in fetuses with tetralogy of Fallot of 25% (95% CI 14%-39). These abnormalities included ventriculomegaly (commonest), agenesis of the corpus callosum, ventricular bleeding, increased extra-axial space, vermian hypoplasia, white matter abnormalities and delayed brain development. Fetuses with CHD were more likely, than those without CHD, to have reduced brain volume, delay in brain maturation and altered brain circulation, most commonly in the form of reduced middle cerebral artery pulsatility index and cerebroplacental ratio. These changes are usually evident in the third trimester, but some studies have reported them as early as the second trimester.

Conclusions: In the absence of known major aneuploidy or genetic syndromes, fetuses with CHD are at increased risk of brain abnormalities, which are present antenatally.

Introduction

Despite advances in obstetric, neonatal and cardiac care, congenital heart defects (CHD) remain the leading cause of infant mortality secondary to birth defects[1]. The improvement in outcomes has led to a shift in focus from cardiac morbidity and mortality towards neurodevelopmental outcome[2-6]. Historically, neurodevelopmental delay in children with CHD was attributed to brain injury during their cardiac surgery[7-10]. However, this assumption may not be true. Studies have reported a high prevalence of brain lesions on neuroimaging[11-15] and a significant risk of neurodevelopmental delay[16-18] before cardiac surgery and in those who did not undergo cardiac surgery. We reported that the incidence of brain lesions on conventional imaging before surgery is 34% in cases of transposition of the great arteries (TGA) and 49% in left-sided heart lesions[19]. Moreover, 40% of these newborns/infants exhibit impaired neurodevelopment[19]. These findings generated animated discussion among fetal medicine specialists and pediatric cardiologists, in particular in relation to TGA, in which the surgical outcome has been very successful. However, these findings are consistent with those of a landmark study investigating the long-term outcome of CHD, where 33% of children 16 years of age with TGA who had undergone the arterial switch operation as infants; had brain MRI abnormalities and 65% received remedial academic or behavioral services[20].

Key questions are whether these brain abnormalities are already present before birth; if so, what is the underlying mechanism, and could prenatal intervention alter the outcome. One possible explanation for the high incidence of brain abnormalities and neurodevelopmental impairment is that these neonates may have suffered the 'injuries' post-natally, for example, when the arterial duct closed[19]. Our previous meta-analysis included newborn and infants, but not fetuses, in order to avoid clinical heterogeneity. Therefore, we could not investigate the prevalence of these abnormalities before birth in fetuses with CHD[19].

Compared to postnatal life, fewer studies have investigated prenatal brain development in fetuses with CHD[21-24]. The prevalence of brain abnormalities demonstrated on fetal MRI was reported to be as high as 39%[22]. The primary aim of this study was to perform a systematic review to quantify the prevalence of brain abnormalities in fetuses with apparently isolated CHD.

Methods

Protocol, eligibility criteria, information sources and search

This review was performed according to a protocol designed a priori and recommended for systematic reviews and meta-analysis[25-27]. MEDLINE (1966 - July 2015), EMBASE (1974 - July 2015) and The Cochrane Library (since inception) including The Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and The Cochrane Central Register of Controlled Trials (CENTRAL) were searched electronically on 18th November 2014, and updated on 6th August 2015 utilizing combinations of the relevant MeSH terms, key words, and word variants for "congenital heart", "cardiac", "neurologic", "MRI", "ultrasound", "neuroimaging", "brain", "outcome" (Supplementary Table 1). No language restrictions were imposed in the search or selection criteria. Reference lists of relevant articles and reviews were hand searched for additional reports. The MOOSE guidelines were followed[27]. The study was registered with the PROSPERO database (Registration number: CRD42015025546, http://www.crd.york.ac.uk/PROSPERO).

Study selection, data collection and data items

Studies were assessed according to the following criteria: population, outcome, study design, gestational age, imaging modality and type of CHD. Studies reporting brain abnormalities or changes on neuroimaging in fetuses with CHD were included. Cases were excluded if they underwent prenatal cardiac surgical intervention, had other structural abnormalities (apart from the heart or the brain) or cases with known genetic/chromosomal anomalies.

All abstracts were reviewed independently by two authors (SB, AK). Agreement about potential relevance was reached by consensus, and full text copies of those papers were obtained. The same two reviewers independently extracted data regarding study characteristics and the outcomes. Inconsistencies were discussed by the reviewers and consensus reached. For those articles in which information was not reported but the methodology was such that this information would have been recorded initially, the authors were contacted (but no information was provided). If more than one study was published for the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations.

The outcomes observed in this systematic review were:

1) Structural brain abnormalities: These include anatomical brain abnormalities, such as periventricular leukomalacia and malformation of cortical development. The detection method was fetal brain MRI as some of the brain abnormalities can be detected by prenatal MRI but not ultrasound. The ascertainment method was postnatal brain imaging or post-mortem examination when performed.

2) Changes in brain volume: These include significantly smaller brain volume when compared to controls (fetuses without CHD) or the gestational age-expected normal range or progressive decline in the brain volume when assessed longitudinally indicating reduced growth rate. The detection methods included fetal brain MRI, 3-D volumetric MRI, 3-D ultrasound and Phase Contrast Magnetic Resonance. The ascertainment method, which was rarely reported in the studies, was postnatal brain imaging when performed.

3) Changes in brain metabolism or maturation: These included changes in the N-acetylaspartate (NAA)/choline, Inositol/Choline or Choline/Creatinine ratios, oxygen saturation (SaO_2) of brain blood supply or cerebral oxygen consumption (VO_2). The detection methods included Magnetic Resonance Spectroscopy and Phase Contrast Magnetic Resonance. The ascertainment method, which was rarely reported in the studies, was postnatal brain imaging when performed.

4) Changes in brain blood flow: These included changes in the middle cerebral artery (MCA) pulsatility index (PI) or resistance index (RI) or their z scores, cerebroplacental ratio (CPR), umbilical to cerebral ratio (U/C), blood flow perfusion blood flow perfusion, fractional moving blood volume, vascularization index (VI) and flow index (FI). The detection methods included Doppler ultrasound, Phase Contrast Magnetic Resonance and 3D Power Doppler ultrasound.

Prospective and retrospective cohort, case-control studies and case series with more than three fetuses with CHD were included. Case reports, conference abstracts and editorials were excluded. Studies reporting data on changes in head size without associated brain changes were excluded to avoid over-interpreting these findings as brain abnormalities. Studies where the data on robust outcomes could be extracted were included.

Risk of bias, summary measures and synthesis of the results

Quality assessment of the included studies was performed using the Strengthening the Reporting of Observational Studies in Epidemiology statement criteria[27]. We used random-effect meta-analyses of proportions to combine data on the prevalence of structural brain abnormalities in fetuses with CHD[28,29]. The small number of studies/cases did not permit meaningful stratified meta-analyses according to the type of CHD, except for Tetralogy of Fallot (TOF). Between-study heterogeneity was assessed using the I^2 statistic[30]. Publication bias was explored using funnel plots and was assessed statistically using Egger test (which uses the actual values of the effect sizes and their precision, rather than ranks)[31]. The assessment of the potential publication bias was problematic because of the low number of individual studies, which strongly limits the reliability of formal tests. Funnel plots displaying the outcome rate from individual studies versus their precision (1/standard error) were carried out with an exploratory aim. Tests for funnel plot asymmetry were not used when the total number of publications included for each outcome was less than ten. In this case, the power of the tests is too low to distinguish chance from real asymmetry[32].

Statistical analyses were performed using Stats Direct (Version 2.7.8, Stats Direct Ltd, 9 Bonville Chase, Altrincham, Cheshire WA14 4QA, UK) statistical software.

Results

The search yielded 1,943 citations; of these, 1883 were excluded by review of the title or abstract, as they did not meet the selection criteria, contain original data, were not relevant or contained postnatal data only (Figure 1). Full manuscripts were retrieved for the remaining 60, and a total of 20 studies (n=1175 cases) were included in the review. Three studies reported data on structural brain abnormalities, while data on altered brain volume, metabolism and blood flow were reported in 7, 3 and 14 studies, respectively (Figure 1). The three studies reporting data on structural brain abnormalities were suitable for inclusion in a meta-analysis (221 cases)

Structural brain abnormalities in fetuses with CHD

Table 1 shows the findings of the studies included that reported structural brain abnormalities. The fetal brain MRI was performed in the second half of pregnancy, ranging from 18 to 39 weeks' gestation. The most commonly reported abnormality was ventriculomegaly (8.6% of the fetuses with CHD). Other abnormalities included malformation or delay of cortical development (4.5%), vermian hypoplasia (1.4%), agenesis of the corpus callosum (ACC) (8.1%), holoprosencephaly (0.5%), cerebellar hypoplasia (0.5%), ventricular bleeding (0.5%), enlarged subarachnoid space (1.9%), germinolytic or periventricular cysts (5.1%)[22-24].

The pooled prevalence of structural brain abnormalities (Figure 2) was 59/221 (28%, 95% CI 18-40%, I^2=63.8%). As the number of cases in most studies is too small to report their findings according to the type of CHD, some studies categorized CHD into groups according to their hemodynamic changes. One study classified these brain abnormalities into malformations (such as ACC, malformation of cortical development and Dandy Walker malformation), acquired lesions (such as periventricular leukomalacia, stroke and white matter injury), and widening of the ventricles and/or outer cerebrospinal fluid (CSF) spaces[22]. Subgroup analysis was possible in cases with TOF, where data from two studies could be pooled[23,24]. The prevalence of structural brain abnormalities in fetuses with TOF (Figure 3) was 10/41 (25%, 95% CI 14-39%).

Changes in brain volume in fetuses with CHD

Table 2 illustrates the findings of the studies included that reported on brain volume changes. Neuroimaging was performed using either fetal brain MRI or 3D/4D ultrasound, and was performed in the second half of the pregnancy in all of the studies except one, in which the ultrasound brain assessment was performed as early as 14 weeks' gestation[33]. Of note is that this was the only study that did not show a different growth pattern in fetuses with CHD when compared with the control group[33]. Pooling of the data reported in these studies was not possible due to the clinical heterogeneity and lack of a consistent method of reporting the data quantitatively. All of these studies had a case-control design and most included mixed types of CHD, except for two studies reporting data on hypoplastic left heart syndrome (HLHS) and TOF[23,34]. Studies reported a significant delay in cortical gyrification, shallower parieto-occipital, cingulate, and calcarine fissures, when compared with controls[34,35].

Changes in brain metabolism or maturation in fetuses with CHD

Table 3 shows the findings of the studies that reported on changes in brain metabolism. Functional brain MRI was performed in the third trimester[21,35,36]. Similar to the brain volume changes, pooling of the data on altered brain metabolism was not possible due to the clinical heterogeneity. However, all three studies were consistent in reporting significantly altered brain metabolism and oxygen saturation in fetuses with CHD[21,35,36]. The reported abnormalities

included a change in the N-acetylaspartate/choline, inositol/choline and choline/creatinine ratios[21,35,36].

Changes in brain blood flow in fetuses with CHD

Table 4 shows the findings of the studies that reported on changes in brain circulation. Circulatory changes were assessed using Doppler ultrasound performed in the second and third trimesters, except for one study in which functional MRI was used[35--48]. The cerebral vessel most commonly studied was the middle cerebral artery (MCA), often combined with the umbilical artery (UA) Doppler as the cerebroplacental ratio (CPR). As both the MCA and UA pulsatility index change with gestational age, some studies adjusted for this potential confounding factor using either Z scores or centiles[35,37-48]. In view of the clinical heterogeneity in the gestational age at assessment, vessel examined, variables reported and types of CHD, pooling of the data was not attempted. However, The CPR was significantly lower in fetuses with CHD when compared to controls in more than half (8/14) of the studies[35,37-41,47,48], while the MCA Doppler was significantly altered in fetuses with CHD when compared to controls in 10/14 studies[35,37,39,41,43,44-48].

Quality assessment of the included studies

The quality of the studies is summarized in Figure 4. Among the studies included in this review, the title, abstract, background, objectives, study design, assessment methods and the interpretation of the studies were appropriately described in 100%. On the other hand, explanation of study size (sample size calculation) was reported in none, and flow diagrams to describe the study population were rarely used. However, statistical methods were described in 90% of these studies. The study setting, recruitment period, eligibility, matching criteria, data variables and summary of the key findings were adequately described in more than 70%. Efforts to address bias and acknowledging the limitations of the study were reported in approximately 50% of studies (Figure 4).

Discussion

Summary of findings

This meta-analysis suggests that CHD is associated with an unexpectedly high prevalence of prenatal structural brain abnormalities, reduced brain volume, delay in brain maturation and altered brain circulation. These changes are illustrated on neuroimaging in the third trimester, but some may be detected as early as the second trimester.

Interpretation of the findings

1. Are the brain abnormalities present before or after birth?

The overall prevalence of structural brain abnormalities is increased, but to a slightly lower degree than we previously reported in newborns/infants with CHD before cardiac surgery or who did not have cardiac surgery[19]. The brain abnormalities reported here during fetal life are similar to those reported after birth, in particular ventriculomegaly, ACC, ventricular bleeding, enlarged subarachnoid space and brain cysts[19].

Both meta-analyses included observational studies, with their inherent risks of bias and possible over- or under-reporting of brain abnormalities in cases with CHD. One main limitation of the previous meta-analysis, which we have addressed in the current review, was the inability to clarify whether the reported brain abnormalities detected on neuroimaging had occurred before or after birth. The fact that the prevalence of brain abnormalities reported in fetuses was slightly lower than that reported in newborns with CHD before or without surgery suggests that peripartum events are unlikely to be the main contributor. The findings of the current systematic review, which was limited to the findings of antenatal neuroimaging, are consistent with those of pathological studies[49,50]. Almost half of babies with HLHS had associated congenital brain abnormalities in pathological studies[49,50]. We did not include pathological studies in this review, in order to avoid clinical heterogeneity.

2. What is the explanation for this association between brain abnormalities and CHD?

Conventionally, G banded karyotyping was used to exclude aneuploidy. However, compared to routine karyotype, up to 6% additional clinically relevant deletions or duplications can be diagnosed in fetuses with a structural anomaly using microarray analysis[51]. In cases with CHD, the incremental yield is as high as 16%[52]. This suggests that undiagnosed chromosomal aberrations could explain the reported association with structural brain abnormalities. Furthermore, in some of the studies the excluded chromosomal abnormalities were limited to 22q11 microdeletion, and trisomy 13, 21, and 18. In the study by Mlczoch and colleagues, chromosomal analysis was not performed in 31/53 cases[22]. Similarly, in 37% of cases reported by Schellen et al there was no genetic work up[23]. However, a recent study reported no difference in brain size and/or oxygenation between syndromic and non-syndromic fetuses with CHD[36], which makes a genetic origin of the observed brain changes unlikely.

An alternative explanation for this association could be altered cerebral circulation in-utero in fetuses with CHD[35,37-47]. This hypothesis is supported by the finding of a higher prevalence of brain lesions amongst babies with left-sided heart lesions in postnatal studies, compared to cases of TGA[19,53,54].

3. Does the association between brain abnormalities and CHD vary according to the type of CHD?

The risk of brain abnormalities detected in neonates/infants before cardiac surgery seems to be greatest in left-sided heart lesions, e.g. HLHS[19]. However, the brain abnormalities and impaired

brain growth reported in fetuses with TOF as early as the second trimester question the assumption that fetuses with right ventricular outflow tract obstruction are less affected by altered cerebral perfusion than fetuses with left-sided heart lesions[23]. In a recent study, the type of the CHD was not significantly associated with the risk of abnormal brain neurodevelopment[35], and prenatal brain changes and childhood developmental delay have also been demonstrated in CHD types that are associated with normal brain perfusion during fetal life[41,55]. Therefore, simply relying on the type of CHD as a predictor of the risk of impaired brain development is not likely to be clinically useful, and larger prospective studies are required.

4. How early can brain abnormalities be detected in fetuses with CHD?

Smaller head size is commonly described in fetuses with CHD[35,47]. As a small head size per se does not necessarily equate to brain abnormalities or neurodevelopmental delay, we have excluded the data on small head size unless it was associated with brain abnormalities. These brain changes can be detected as early as 25 weeks' gestation, and as early as 20 weeks in TOF[23,34]. This altered brain development might be already present in affected fetuses as early as 20 weeks, and degenerative changes in the developing cortex become increasingly apparent during the late third trimester[21,34].

Strengths and limitations of the systematic review

The quality of the data available for meta-analysis limits the current study findings. Small numbers and selection bias of retrospective reviews were the general drawbacks. With specific reference to the type of CHD, the lack of extractable data on clinical sub-groups of CHD and the clinical heterogeneity among the studies are likely to have resulted in under- or over-reporting of these adverse outcomes.

Clinical and research implications of the review findings

There is growing evidence indicating a prenatal effect of CHD on brain development, implying that postnatal neuroprotective interventions are likely to be of limited value. An important question is whether the delay in brain growth, development and maturation result in significant neurodevelopmental delay and, if so, whether it might be possible to identify those fetuses at increased risk and ultimately improve the postnatal outcome. Firstly, Bayley Scales of Infant and Toddler Development (BSID-III) average scores were found to be significantly correlated to total brain volume, cingulated fissure depth, inositol/choline and N-acetylaspartate/ choline ratios[35]. Secondly, cerebrovascular resistance is associated with higher neurodevelopmental scores in fetuses with single ventricle anomalies[56]. Thirdly, brain dysmaturation is associated with increased susceptibility to white matter injury. Fourthly, these brain changes can potentially be detected as early as 25 weeks' gestations, but more importantly, hemodyamic brain changes recorded as early as 20 weeks can identify those fetuses who will manifest delayed brain growth and maturation, and ultimately those who will suffer from neurodevelopmental impairment[35]. A more exciting finding recently reported by Sun et al, is a proposed direct link between reduced cerebral oxygenation and impaired brain growth in fetuses with CHD, which raises the possibility of an improvement of the in utero brain development using maternal oxygen therapy[36].

Based on the findings of this meta-analysis, we would recommend a prospective longitudinal study where cases with CHD have brain fetal MRI in the third trimester, and after birth, close periodic developmental surveillance follow-up. Despite the fact that the American Heart Association recommends periodic developmental surveillance, screening, evaluation, and reevaluation throughout childhood in children with CHD[57], it is not currently routine to screen for brain abnormalities or neurodevelopmental delay in newborns with CHD. The evidence from this meta-analysis and other studies calls for a policy which recommends early assessment of these cases, starting from fetal life. Finally, the identification of significant brain abnormalities during

fetal life might also influence the parents' decision following antenatal counseling. In response to these findings the International society of Ultrasound in Obstetrics and Gynecology (ISUOG) is developing a consensus on how these pregnancies should be counseled prenatally, including conveying these findings and the limitations of the published literature.

Funding source: none

References

1. Mensah GA and Brown DW. An Overview Of Cardiovascular Disease Burden In The United States. *Health Affairs* 2007; **26**: 38-48.

2. Hoffman J, Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol* 2002; **39**: 1890-1900.

3. Knowles RL, Bull C, Wren C, Dezateux C. Mortality with congenital heart defects in England and Wales, 1959-2009: exploring technological change through period and birth cohort analysis. *Arch Dis Child* 2012; **97**: 861-865

4. Wernovsky G. Outcomes regarding the central nervous system in children with complex congenital cardiac malformations. *Cardiol Young* 2005; **15**(Suppl 1): 132-133.

5. Donofrio MT, Massaro AN. Impact of congenital heart disease on brain development and neurodevelopmental outcome. *Int J Pediatr* 2010; 2010. pii: 359390. doi: 10.1155/2010/359390.

6. Donofrio MT, Duplessis AJ, Limperopoulos C. Impact of congenital heart disease on fetal brain development and injury. *Curr Opin Pediatr* 2011; **23**: 502-511.

7. Burrows F, Hillier SC, McLeod ME, Iron KS, Taylor MJ. Anterior fontanel pressure and visual evoked potentials in neonates and infants undergoing profound hypothermic circulatory arrest. *Anesthesiology* 1990; **73**: 632-636.

8. Newburger J, Jonas RA, Wernovsky G, David Wypij, Hickey PR, Kuban K, Farrell DM, Holmes GL, Helmers SL, Constantinou J, Carrazana E, Barlow JK, Walsh AZ, Lucius KC, Share JC, Wessel DL, Hanley FL, Mayer JE, Jr., Castaneda AR, and Ware JH. A comparison of the perioperative neurologic effects of hypothermic circulatory arrest versus low-flow cardiopulmonary bypass in infant heart surgery. *N Engl J Med* 1993; **329**: 1057-1064.

9. O'Hare B, Bissonnette B, Bohn D, Cox P, Williams W. Persistent low cerebral blood flow velocity following profound hypothermic circulatory arrest in infants. *Can J Anesthesia* 1995; **42**: 964-971.

10. Ferry PC. Neurologic sequelae of open-heart surgery in children. *Am J Dis Child* 1990; **144**: 369-373.

11. Beca J, Gunn J, Coleman L, Hope A, Whelan LC, Gentles T, Inder T, Hunt R, Shekerdemian L. Pre-operative brain injury in newborn infants with transposition of the great arteries occurs at rates similar to other complex congenital heart disease and is not related to balloon atrial septosomy. *J Am Coll Cardiol* 2009; **553**: 1807-1811.

12. Licht D, Wang J, Silvestre DW, Nicolson SC, Montenegro LM, Wernovsky G, Tabbutt S, Durning SM, Shera DM, Gaynor JW, Spray TL, Clancy RR, Zimmerman RA, Detre JA. Preoperative cerebral blood flow is diminished in neonates with severe congenital heart defects. *J Thorac Cardiovasc Surg* 2004; **128**: 841-849.

13. Licht D, Shera DM, Clancy RR, Wernovsky G, Montenegro LM, Nicolson SC, Zimmerman RA, Spray TL, Gaynor JW, Vossough A. Brain maturation is delayed in infants with complex congenital heart defects. *J Thorac Cardiovasc Surg* 2009; **137**: 529-537.

14. Mahle W, Tavani F, Zimmerman RA, Nicolson SC, Galli KK, Gaynor JW, Clancy RR, Montenegro LM, Spray TL, Chiavacci RM, Wernovsky G, Kurth CD. An MRI study of neurological injury before and after congenital heart surgery. *Circulation* 2002; **106**(Suppl I): I109-I114.

15. Miller S, McQuillen PS, Hamrick S, Xu D, Glidden DV, Charlton N, Karl T, Azakie A, Ferriero DM, Barkovich AJ, Vigneron DB. Abnormal brain development in newborns with congenital heart disease. *N Engl J Med* 2007; **357**: 1928-1938.

16. Limperopoulos C, Majnemer A, Shevell MI, Rosenblatt B, Rohlicek C, Tchervenkov C. Neurologic status of newborns with congenital heart defects before open heart surgery. *Pediatrics* 1999; **103**: 402-408.

17. Limperopoulos C, Majnemer A, Shevell MI, Rosenblatt B, Rohlicek C, Tchervenkov C. Neurodevelopmental status of newborns and infants with congenital heart defects before and after open heart surgery. *J Pediatr* 2000; **137**: 638-645.

18. Miller S, McQuillen PS, Vigneron DB, Glidden DV, Barkovich AJ, Ferriero DM, Hamrick SE, Azakie A, Karl TR. Preoperative brain injury in newborns with transposition of the great arteries. *Ann Thorac Surg* 2004; **77**: 1698-1706.

19. Khalil A, Suff N, Thilaganathan B, Hurrell A, Cooper D, Carvalho JS. Brain abnormalities and neurodevelopmental delay in congenital heart disease: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2014; **43**: 14-24.

20. Bellinger DC, Wypij D, Rivkin MJ, DeMaso DR, Robertson RL Jr, Dunbar-Masterson C, Rappaport LA, Wernovsky G, Jonas RA, Newburger JW. Adolescents with d-transposition of the great arteries corrected with the arterial switch procedure: neuropsychological assessment and structural brain imaging. *Circulation* 2011; **124**: 1361-1369.

21. Limperopoulos C, Tworetzky W, McElhinney DB, Newburger JW, Brown DW, Robertson RL Jr, Guizard N, McGrath E, Geva J, Annese D, DunbarMasterson C, Trainor B, Laussen PC, du Plessis AJ. Brain volume and metabolism in fetuses with congenital heart disease: evaluation with quantitative magnetic resonance imaging and spectroscopy. *Circulation* 2010; **121**: 26-33.

22. Mlczoch E, Brugger P, Ulm B, Novak A, Frantal S, Prayer D, Salzer-Muhar U. Structural congenital brain disease in congenital heart disease: results from a fetal MRI program. *Eur J Paediatr Neurol* 2013; **17**: 153-160.

23. Schellen C, Ernst S, Gruber GM, Mlczoch E, Weber M, Brugger PC, Ulm B, Langs G, Salzer-Muhar U,Prayer D, Kasprian G. Fetal MRI detects early alterations of brain development in Tetralogy of Fallot. *Am J Obstet Gynecol* 2015; **213**: 392.e1-7.

24. Brossard-Racine M, du Plessis AJ, Vezina G, Robertson R, Bulas D, Evangelou IE, Donofrio M, Freeman D, Limperopoulos C. Prevalence and spectrum of

in utero structural brain abnormalities in fetuses with complex congenital heart disease. *Am J Neuroradiol* 2014; **35**: 1593-1599.

25. Henderson LK, Craig JC, Willis NS, Tovey D, Webster AC. How to write a Cochrane systematic review. *Nephrology* (Carlton) 2010; **15**: 617–624.

26. NHS Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care. York (UK): University of York; 2009.

27. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; **283**: 2008–2012.

28. Manzoli L, De Vito C, Salanti G, D'Addario M, Villari P, Ioannidis JP. Meta-analysis of the immunogenicity and tolerability of pandemic influenza A 2009 (H1N1) vaccines. *PLoS One* 2011; **6**:e24384.

29. Hunter JP, Saratzis A, Sutton AJ, Boucher RH, Sayers RD, Bown MJ. In meta-analyses of proportion studies, funnel plots were found to be an inaccurate method of assessing publication bias. *J Clin Epidemiol* 2014; **67**: 897–903.

30. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557-560.

31. Sterne JAC, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *J Clin Epidemiol* 2001; **54**: 1045–1046.

32. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 [updated September 2009]. The Cochrane Collaboration; 2009 [www.cochrane-handbook.org].

33. Schiessl B, Fakler U, Vogt M, Friese K, Hess J, Oberhoffer R. 3-Dimensional sonographic volumetry of fetal brain, liver and myocardial mass--interdisciplinary clinical validation of the method and application in fetuses with and without structural heart disease. *Z Geburtshilfe Neonatol* 2011; **215**: 60-68.

34. Clouchoux C, du Plessis AJ, Bouyssi-Kobar M, Tworetzky W, McElhinney DB, Brown DW, Gholipour A, Kudelski D, Warfield SK, McCarter RJ, Robertson RL Jr, Evans AC, Newburger JW, Limperopoulos C. Delayed cortical development in fetuses with complex congenital heart disease. *Cereb Cortex* 2013; **23**: 2932-2943.

35. Masoller N, Sanz-Cortés M, Crispi F, Gómez O, Bennasar M, Egaña-Ugrinovic G, Bargalló N, Martínez JM, Gratacós E. Fetal brain Doppler and biometry at mid-gestation for the early prediction of abnormal brain development at birth in congenital heart disease. *Ultrasound Obstet Gynecol* 2015. doi: 10.1002/uog.14919. [Epub ahead of print]

36. Sun L, Macgowan CK, Sled JG, Yoo SJ, Manlhiot C, Porayette P, Grosse-Wortmann L, Jaeggi E, McCrindle BW, Kingdom J, Hickey E, Miller S, Seed M. Reduced fetal cerebral oxygen consumption is associated with smaller brain size in fetuses with congenital heart disease. *Circulation* 2015; **131**: 1313-1323.

37. Chen Y, Lv G, Li B, Wang Z. Cerebral vascular resistance and left ventricular myocardial performance in fetuses with Ebstein's anomaly. *Am J Perinatol* 2009; **26**: 253-258.
38. Guorong L, Shaohui L, Peng J, Huitong L, Boyi L, Wanhong X, Liya L. Cerebrovascular blood flow dynamic changes in fetuses with congenital heart disease. *Fetal Diagn Ther* 2009; **25**: 167-172.

39. Itsukaichi M, Kikuchi A, Yoshihara K, Serikawa T, Takakuwa K, Tanaka K. Changes in fetal circulation associated with congenital heart disease and their effects on fetal growth.. *Fetal Diagn Ther* 2011; **30**: 219-224.
40. Berg C, Gembruch O, Gembruch U, Geipel A. Doppler indices of the middle cerebral artery in fetuses with cardiac defects theoretically associated with impaired cerebral oxygen delivery in utero: is there a brain-sparing effect? *Ultrasound Obstet Gynecol* 2009; **34**: 666-672.

41. Donofrio MT, Bremer YA, Schieken RM, Gennings C, Morton LD, Eidem BW, Cetta F, Falkensammer CB, Huhta JC, Kleinman CS. Autoregulation of cerebral blood flow in fetuses with congenital heart disease: the brain sparing effect. *Pediatr Cardiol* 2003; **24**: 436-443.

42. Modena A, Horan C, Visintine J, Chanthasenanont A, Wood D, Weiner S. Fetuses with congenital heart disease demonstrate signs of decreased cerebral impedance. *Am J Obstet Gynecol* 2006; **195**: 706-710.

43. Kaltman JR, Di H, Tian Z, Rychik J. Impact of congenital heart disease on cerebrovascular blood flow dynamics in the fetus. *Ultrasound Obstet Gynecol* 2005; **25**: 32-36.

44. Jouannic JM, Benachi A, Bonnet D, Fermont L, Le Bidois J, Dumez Y, Dommergues M. Middle cerebral artery Doppler in fetuses with transposition of the great arteries. *Ultrasound Obstet Gynecol* 2002; **20**: 122-124.

45. Zeng S, Zhou J, Peng Q, Tian L, Xu G, Zhao Y, Wang T, Zhou Q. Assessment by three-dimensional power Doppler ultrasound of cerebral blood flow perfusion in fetuses with congenital heart disease. *Ultrasound Obstet Gynecol* 2015; **45**: 649-656.

46. Zeng S, Zhou QC, Zhou JW, Li M1, Long C, Peng QH. Volume of intracranial structures on three-dimensional ultrasound in fetuses with congenital heart disease. *Ultrasound Obstet Gynecol* 2015; **46**: 174-1781.

47. Masoller N, Martínez JM, Gómez O, Bennasar M, Crispi F, Sanz-Cortés M, Egaña-Ugrinovic G, Bartrons J, Puerto B, Gratacós E. Evidence of second-trimester changes in head biometry and brain perfusion in fetuses with congenital heart disease. *Ultrasound Obstet Gynecol* 2014; **44**: 182-187.

48. Yamamoto Y, Khoo NS, Brooks PA, Savard W, Hirose A, Hornberger LK. Severe left heart obstruction with retrograde arch flow influences fetal cerebral and placental blood flow. *Ultrasound Obstet Gynecol* 2013; **42**: 294-299.

49. Glauser TA, Rorke LB, Weinberg PM, Clancy RR. Acquired neuropathologic lesions associated with the hypoplastic left heart syndrome. *Pediatrics* 1990; **85**: 991–1000.
50. Glauser TA, Rorke LB, Weinberg PM, Clancy RR. Congenital brain abnormalities associated with the hypoplastic left heart syndrome. *Pediatrics* 1990; **85**: 984–990.
51. Wapner RJ, Martin CL, Levy B, Ballif BC, Eng CM, Zachary JM, Savage M, Platt LD, Saltzman D, Grobman WA, Klugman S, Scholl T, Simpson JL, McCall K, Aggarwal VS, Bunke B, Nahum O, Patel A, Lamb AN, Thom EA, Beaudet AL, Ledbetter DH, Shaffer LG, Jackson L. Chromosomal microarray versus karyotyping for prenatal diagnosis. *N Engl J Med* 2012; **367**: 2175-2184.
52. Donnelly JC, Platt LD, Rebarber A, Zachary J, Grobman WA, Wapner RJ. Association of copy number variants with specific ultrasonographically detected fetal anomalies. *Obstet Gynecol* 2014; **124**: 83-90.
53. Frasch MG, Müller T, Wicher C, Weiss C, Löhle M, Schwab K, Schubert H, Nathanielsz PW, Witte OW, Schwab M. Fetal body weight and the development of the control of the cardiovascular system in fetal sheep. *J Physiol* 2007; **579**: 893-907.
54. Hutter D, Kingdom J, Jaeggi E. Causes and mechanisms of intrauterine hypoxia and its impact on the fetal cardiovascular system: a review. Int J Pediatr 2010;2010:401323.
55. Majnemer A, Limperopoulos C, Shevell MI, Rohlicek C, Rosenblatt B, Tchervenkov C. A New Look at Outcomes of Infants With Congenital Heart Disease. *Pediatr Neurol* 2009; **40**: 197–204
56. Williams IA, Fifer C, Jaeggi E, Levine JC, Michelfelder EC, Szwast AL. The association of fetal cerebrovascular resistance with early neurodevelopment in single ventricle congenital heart disease. *Am Heart J* 2013; **165**: 544-550.e1.
57. Marino BS, Lipkin PH, Newburger JW, Peacock G, Gerdes M, Gaynor JW, Mussatto KA, Uzark K, Goldberg CS, Johnson WH Jr, Li J, Smith SE, Bellinger DC, Mahle WT; American Heart AssociationCongenital Heart Defects Committee, Council on Cardiovascular Disease in the Young, Council on Cardiovascular Nursing, and Stroke Council. Neurodevelopmental Outcomes in Children With Congenital Heart Disease: Evaluation and Management A Scientific Statement From the American Heart Association. *Circulation* 2012; **126**: 1143-1172.

Supplementary_Table 1. Search strategy using Medline, Embase and The Cochrane Library (since inception) including The Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and The Cochrane Central Register of Controlled Trials (CENTRAL).

Databases**:** Embase®, Embase® Alert, MEDLINE®

Set#	Searched for	Results
S15	**s13 or s14**	**1719**
S14	((s1 or s2 or s3) and (s4 or s5 or s6) and (s7 or s8 or s9 or s10 or s11)) not (animal(yes) or EMB.EXACT("nonhuman"))	1537
S13	(s1 or s2 or s3) and (s4 or s5 or s6) and (s7 or s8 or s9 or s10 or s11) and human(yes)	1621
S12	(s1 or s2 or s3) and (s4 or s5 or s6) and (s7 or s8 or s9 or s10 or s11)	1811
S11	ti,ab(fetus[*2] or foetus[*2] or fetal[*2] or foetal[*2] or prenatal[*2] or "pre natal[*2]" or prepartal[*2] or "pre partal[*2]" or prepartum[*1] or "pre partum[*1]" or antenatal[*2] or "ante natal[*2]" or antepartal[*2] or "ante partal[*2]" or antepartum[*1] or "ante partum[*1]" or "in utero" or intrauterine or "intra uterine" or uterine or preimplant[*6] or "pre implant[*6]" or fetalis or foetalis or pregnan[*4] or trimester[*1])	1627149
S10	EMB.EXACT("fetomaternal transfusion") OR EMB.EXACT("intrauterine growth retardation") OR EMB.EXACT.EXPLODE("prenatal diagnosis") OR EMB.EXACT("prenatal development") OR EMB.EXACT("prenatal stress") OR EMB.EXACT("prenatal injury") OR EMB.EXACT("prenatal disorder") OR EMB.EXACT("prenatal period") OR EMB.EXACT("prenatal drug exposure") OR EMB.EXACT("prenatal exposure") OR EMB.EXACT("prenatal growth") OR EMB.EXACT("prenatal mortality") OR EMB.EXACT("prenatal screening") OR EMB.EXACT("prenatal care") OR EMB.EXACT.EXPLODE("pregnancy") OR EMB.EXACT.EXPLODE("multiple pregnancy") OR EMB.EXACT("prolonged pregnancy") OR EMB.EXACT("pregnancy complication") OR EMB.EXACT("high risk pregnancy") OR EMB.EXACT.EXPLODE("ectopic pregnancy") OR EMB.EXACT("pregnancy disorder") OR EMB.EXACT("pregnancy outcome") OR EMB.EXACT("pregnancy rate") OR EMB.EXACT("early pregnancy factor") OR EMB.EXACT("pregnant woman")	885654
S9	EMB.EXACT("fetus") OR EMB.EXACT("fetus outcome") OR EMB.EXACT.EXPLODE("fetus maturity") OR EMB.EXACT.EXPLODE("fetus development") OR EMB.EXACT("fetus hypoxia") OR EMB.EXACT("fetus	297644

	disease") OR EMB.EXACT("fetus distress") OR EMB.EXACT("fetus malformation") OR EMB.EXACT.EXPLODE("fetus function test") OR EMB.EXACT.EXPLODE("fetus echography") OR EMB.EXACT.EXPLODE("fetus control") OR EMB.EXACT("fetus heart rate") OR EMB.EXACT("fetus monitoring") OR EMB.EXACT("fetus blood") OR EMB.EXACT("fetus heart") OR EMB.EXACT.EXPLODE("fetus (anatomy)") OR EMB.EXACT("fetus circulation") OR EMB.EXACT("fetus growth") OR EMB.EXACT("fetus mortality") OR EMB.EXACT("fetus movement") OR EMB.EXACT("fetus resorption") OR EMB.EXACT("fetus death") OR EMB.EXACT("fetus wastage") OR EMB.EXACT("fetus risk") OR EMB.EXACT("fetus weight") OR EMB.EXACT("fetal hemorrhage") OR EMB.EXACT("fetotoxicity")	
S8	MESH.EXACT.EXPLODE("Prenatal Diagnosis") OR MESH.EXACT.EXPLODE("Ultrasonography, Prenatal") OR MESH.EXACT("Prenatal Exposure Delayed Effects") OR MESH.EXACT("Prenatal Injuries") OR MESH.EXACT("Prenatal Care") OR MESH.EXACT("Uterine Monitoring") OR MESH.EXACT("Pregnancy") OR MESH.EXACT("Pregnancy Complications") OR MESH.EXACT("Pregnancy Rate") OR MESH.EXACT.EXPLODE("Pregnancy Trimesters") OR MESH.EXACT("Pregnancy, High-Risk") OR MESH.EXACT.EXPLODE("Pregnancy, Multiple") OR MESH.EXACT("Pregnancy, Heterotopic") OR MESH.EXACT("Pregnancy, Prolonged") OR MESH.EXACT.EXPLODE("Pregnancy, Ectopic") OR MESH.EXACT("Pregnant Women") OR MESH.EXACT("Pregnancy, Unplanned") OR MESH.EXACT("Pregnancy, Unwanted")	715455
S7	MESH.EXACT.EXPLODE("Fetal Monitoring") OR MESH.EXACT.EXPLODE("Fetal Heart") OR MESH.EXACT.EXPLODE("Fetus") OR MESH.EXACT("Fetal Diseases") OR MESH.EXACT("Fetal Viability") OR MESH.EXACT("Fetal Movement") OR MESH.EXACT("Fetal Development") OR MESH.EXACT("Fetal Weight") OR MESH.EXACT("Fetal Organ Maturity") OR MESH.EXACT("Fetal Blood") OR MESH.EXACT("Fetal Death") OR MESH.EXACT("Fetal Resorption") OR MESH.EXACT("Fetal Distress") OR MESH.EXACT("Fetal Growth Retardation") OR MESH.EXACT("Fetal Hypoxia") OR MESH.EXACT("Fetal Mortality") OR MESH.EXACT("Heart Rate, Fetal") OR MESH.EXACT("Maternal-Fetal Exchange")	213787
S6	ti,ab((brain* or cranial or cerebral or cerebell* or craniocerebral or intracerebral or intracranial) near/5 (malform* or abnormal* or anomaly or anomalies or defect* or dysfunction* or develop[*5] or maturation* or maturity or impair* or delay* or function* or size or volume or growth or structur[*2] or microstructur[*2] or bleed* or microbleed* or hemorrhag* or microhemorrhag* or haemorrhag* or microhaemorrhag* or impedance or damage* or injury or injuries or trauma*))	721929

S5	EMB.EXACT("brain malformation") OR EMB.EXACT("brain development") OR EMB.EXACT("nervous system development") OR EMB.EXACT("brain maturation") OR EMB.EXACT("brain dysfunction") OR EMB.EXACT("brain function") OR EMB.EXACT("brain size") OR EMB.EXACT("brain growth") OR EMB.EXACT.EXPLODE("brain metabolism") OR EMB.EXACT.EXPLODE("brain hemorrhage") OR EMB.EXACT("brain damage") OR EMB.EXACT("traumatic brain injury") OR EMB.EXACT("cerebellum injury") OR EMB.EXACT("brain injury")	372889
S4	MESH.EXACT.EXPLODE("Brain -- abnormalities") OR MESH.EXACT("Brain -- pathology") OR MESH.EXACT("Brain -- physiopathology") OR MESH.EXACT("Brain -- growth & development") OR MESH.EXACT("Brain Damage, Chronic") OR MESH.EXACT("Brain Injury, Chronic") OR MESH.EXACT("Brain Injuries") OR MESH.EXACT("Brain -- injuries") OR MESH.EXACT.EXPLODE("Cerebral Hemorrhage") OR MESH.EXACT("Intracranial Hemorrhages") OR MESH.EXACT("Intracranial Hemorrhage, Traumatic") OR MESH.EXACT.EXPLODE("Brain Hemorrhage, Traumatic") OR MESH.EXACT.EXPLODE("Subarachnoid Hemorrhage")	223671
S3	ti,ab(congenital* near/3 (heart or cardiac)) or ti,ab((heart or cardiac) near/3 defect*) or ti,ab((heart or cardiac) near/3 abnormalit*) or ti,ab((heart or cardiac) near/3 malform*) or ti,ab((heart or cardiac) near/3 (anomaly or anomalies)) or ti,ab((aortic or aorta) near/3 coarct*) or ti,ab(transpos[*6] near/3 (arteries or artery or vessel[*1])) or ti,ab(double near/3 outlet near/3 ventricle[*1]) or ti,ab(heart near/3 hypoplas*) or ti,ab((septal or septum) near/3 defect*) or ti,ab(paten[*2] near/3 ductus near/3 arteriosus) or ti,ab(fallot[*1] near/3 (tetralogy or trilogy)) or ti,ab(cyanotic near/3 (heart or cardiac))	209511
S2	EMB.EXACT.EXPLODE("congenital heart malformation") OR EMB.EXACT.EXPLODE("congenital heart disease") OR EMB.EXACT.EXPLODE("heart disease -- congenital disorder") OR EMB.EXACT("aorta coarctation") OR EMB.EXACT.EXPLODE("great vessels transposition")	162526
S1	MESH.EXACT.EXPLODE("Heart Defects, Congenital") OR MESH.EXACT.EXPLODE("Heart Diseases -- congenital")	124348

Databases:

- The Cochrane Database of Systematic Reviews (CDSR, Cochrane Reviews: Issue 11 of 12, November 2014) (2 references)
- Database of Abstracts of Reviews of Effects (DARE, Other Reviews: Issue 4 of 4, October 2014) (0 references)

- The Cochrane Central Register of Controlled Trials (CENTRAL, Trials: Issue 10 of 12, October 2014) (16 references)
- Health Technology Assessment Database (HTA, Technology Assessments: Issue 4 of 4, October 2014) (0 references)
- NHS Economic Evaluation Database (NHS-EED, Economic Evaluations: Issue 4 of 4, October 2014) (0 references)

ID	Search	Hits
#1	MeSH descriptor: [Heart Defects, Congenital] explode all trees	1541
#2	MeSH descriptor: [Heart Diseases] explode all trees and with qualifiers: [Congenital - CN]	22
#3	(congenital* near/3 (heart or cardiac)):ti,ab,kw	880
#4	((heart or cardiac) near/3 defect*):ti,ab,kw	842
#5	((heart or cardiac) near/3 abnormalit*):ti,ab,kw	233
#6	((heart or cardiac) near/3 malform*):ti,ab,kw	33
#7	((heart or cardiac) near/3 (anomaly or anomalies)):ti,ab,kw	29
#8	((aortic or aorta) near/3 coarct*):ti,ab,kw	55
#9	(transpos* near/3 (arteries or artery or vessel*)):ti,ab,kw	67
#10	(double near/3 outlet near/3 ventricle*):ti,ab,kw	7
#11	(heart near/3 hypoplas*):ti,ab,kw	57
#12	((septal or septum) near/3 defect*):ti,ab,kw	333
#13	(paten* near/3 ductus near/3 arteriosus):ti,ab,kw	494
#14	(fallot* near/3 (tetralogy or trilogy)):ti,ab,kw	105
#15	(cyanotic near/3 (heart or cardiac)):ti,ab,kw	52
#16	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15	2502
#17	MeSH descriptor: [Brain] explode all trees and with qualifiers: [Abnormalities - AB]	24
#18	MeSH descriptor: [Brain] this term only and with qualifiers: [Pathology - PA]	642

#19	MeSH descriptor: [Brain] this term only and with qualifiers: [Physiopathology - PP]	654
#20	MeSH descriptor: [Brain] this term only and with qualifiers: [Growth & development - GD]	65
#21	MeSH descriptor: [Brain Damage, Chronic] this term only	240
#22	MeSH descriptor: [Brain Injury, Chronic] this term only	26
#23	MeSH descriptor: [Brain Injuries] this term only	997
#24	MeSH descriptor: [Cerebral Hemorrhage] explode all trees	684
#25	MeSH descriptor: [Intracranial Hemorrhages] this term only	158
#26	MeSH descriptor: [Intracranial Hemorrhage, Traumatic] this term only	13
#27	MeSH descriptor: [Brain Hemorrhage, Traumatic] explode all trees	9
#28	MeSH descriptor: [Subarachnoid Hemorrhage] explode all trees	454
#29	((brain* or cranial or cerebral or cerebell* or craniocerebral or intracerebral or intracranial) near/5 (malform* or abnormal* or anomaly or anomalies or defect* or dysfunction* or develop* or maturation* or maturity or impair* or delay* or function* or size or volume or growth or structur* or microstructur* or bleed* or microbleed* or hemorrhag* or microhemorrhag* or haemorrhag* or microhaemorrhag* or impedance or damage* or injury or injuries or trauma*)):ti,ab,kw	10382
#30	#17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29	11446
#31	#16 and #30	159
#32	MeSH descriptor: [Fetal Monitoring] explode all trees	357
#33	MeSH descriptor: [Fetal Heart] explode all trees	115
#34	MeSH descriptor: [Fetus] explode all trees	1520
#35	MeSH descriptor: [Fetal Diseases] this term only	177
#36	MeSH descriptor: [Fetal Viability] this term only	7
#37	MeSH descriptor: [Fetal Movement] this term only	62
#38	MeSH descriptor: [Fetal Development] this term only	61
#39	MeSH descriptor: [Fetal Weight] this term only	18

#40	MeSH descriptor: [Fetal Organ Maturity] this term only	42
#41	MeSH descriptor: [Fetal Blood] this term only	543
#42	MeSH descriptor: [Fetal Death] this term only	208
#43	MeSH descriptor: [Fetal Resorption] this term only	1
#44	MeSH descriptor: [Fetal Distress] this term only	128
#45	MeSH descriptor: [Fetal Growth Retardation] this term only	273
#46	MeSH descriptor: [Fetal Hypoxia] this term only	26
#47	MeSH descriptor: [Fetal Mortality] this term only	6
#48	MeSH descriptor: [Heart Rate, Fetal] this term only	317
#49	MeSH descriptor: [Maternal-Fetal Exchange] this term only	314
#50	MeSH descriptor: [Prenatal Diagnosis] explode all trees	936
#51	MeSH descriptor: [Ultrasonography, Prenatal] explode all trees	494
#52	MeSH descriptor: [Prenatal Exposure Delayed Effects] this term only	252
#53	MeSH descriptor: [Prenatal Injuries] this term only	1
#54	MeSH descriptor: [Prenatal Care] this term only	1062
#55	MeSH descriptor: [Uterine Monitoring] this term only	17
#56	MeSH descriptor: [Pregnancy] this term only	63
#57	MeSH descriptor: [Pregnancy Complications] this term only	1161
#58	MeSH descriptor: [Pregnancy Rate] this term only	1143
#59	MeSH descriptor: [Pregnancy Trimesters] explode all trees	1473
#60	MeSH descriptor: [Pregnancy, High-Risk] this term only	188
#61	MeSH descriptor: [Pregnancy, Multiple] explode all trees	204
#62	MeSH descriptor: [Pregnancy, Heterotopic] this term only	0
#63	MeSH descriptor: [Pregnancy, Prolonged] this term only	113
#64	MeSH descriptor: [Pregnancy, Ectopic] explode all trees	172

#65	MeSH descriptor: [Pregnant Women] this term only	97
#66	MeSH descriptor: [Pregnancy, Unplanned] this term only	56
#67	MeSH descriptor: [Pregnancy, Unwanted] this term only	43
#68	(fetus* or foetus* or fetal* or foetal* or prenatal* or "pre natal*" or prepartal* or "pre partal*" or prepartum* or "pre partum*" or antenatal* or "ante natal*" or antepartal* or "ante partal*" or antepartum* or "ante partum*" or "in utero" or intrauterine or "intra uterine" or uterine or preimplant* or "pre implant*" or fetalis or foetalis or pregnan* or trimester*):ti,ab,kw	34596
#69	#32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68	34773
#83	**#16 and #30 and #69**	**18**

Table 1. Summary of the studies included which reported structural brain abnormalities in fetuses with Congenital Heart Defects (CHD).

Author, year and origin	Study Design Data collection	CHD diagnosis	Gestational age at assessment (weeks)	CHD (n)	Assessment method	Findings
Mlczoch *et al*. 2013[22] Austria	Cohort Retrospective	Mixed[a]	Range 20-37 (mean 28)	53	MRI	**Total abnormalities: 39.6% (21/53)** Malformations 7 (malformation of cortical development 3, agenesis of the corpus callosum 2, holoprosencephaly 1, cerebellar hypoplasia 1), acquired lesions 5 (ventriculomegaly 1, ventricular bleeding 1, enlarged subarachnoidal spaces 1, germinolytic cysts 2) and asymmetric widening of ventricles and/or outer CSF spaces 9 (asymmetry of the ventricles 7, arachnoid cyst and enlarged cisterna magna 2).
Brossard-Racine *et al.* 2014[24] USA/Canada	Case-control Prospective*	Mixed[b]	Range 18-39 (mean 30.61±4.67)	144 (194 controls)	MRI	**Total abnormalities: 22.9% (33/144)** Ventriculomegaly 13, increased extra-axial space 10, vermian hypoplasia 3, periventricular cysts 2, white matter signal hyperintensity 2, cerebral cortical immaturity 3. The most common abnormalities were mild unilateral ventriculomegaly in 12/33 (36.4%) and increased extra-axial spaces in 10/33 (30.3%).
Schellen *et al*. 2015[23] Austria	Case-control Retrospective	TOF	Mean±SD: 25.7±3.6 weeks (median 25.1) in cases and 25.6±3.6 weeks (median 25.0) in the controls	24 (24 controls)	MRI	**Total abnormalities: 21% (5/24)** Ventriculomegaly was observed in 5 of 24 fetuses (21%) with TOF: bilateral mild ventriculomegaly was found in 3 of 24 fetuses (13%); unilateral mild ventriculomegaly was found in 1 of 24 fetuses (4%); and a combination of mild and moderate ventriculomegaly was found in another 1 of 24 fetuses (4%). Ventriculomegaly occurred in none of the control fetuses.

CSF: cerebroplacental fluid; TOF: Tetralogy of Fallot; SD: standard deviation; MRI: magnetic resonance imaging.

Table 2. Summary of the studies included which reported changes in brain volume in fetuses with Congenital Heart Defects (CHD).

Author, year and origin	Study Design Data collection	CHD diagnosis	Gestational age at assessment (weeks)	CHD assessed	Assessment method	Findings
Limperopoulos *et al.* 2010[21] USA/Canada	Case-control Prospective	Mixed[c]	Range 25-37 (median 30)	50	3-D volumetric MRI	Progressive decline in age-adjusted TBV and ICV.
Schiessl *et al.* 2011[33] Germany	Case-control Prospective	Mixed[f]	14-38	39	3D/4D ultrasound	Brain volumes did not show a different growth pattern in fetuses with CHD when compared with the control group.
Clouchoux *et al.* 2013††[34] USA/Canada	Case-control Prospective	HLHS	25.4 – 37.0	18	MRI	Progressive third trimester fall-off in cortical gray and white matter volumes (P<0.001), and subcortical gray matter (P<0.05) in fetuses with HLHS. Significant delays in cortical gyrification were also evident in HLHS fetuses (P<0.001). In the HLHS fetus, local cortical folding delays were detected as early as 25 weeks in the frontal, parietal, calcarine, temporal, and collateral regions and appear to precede volumetric brain growth disturbances.
Zeng *et al.* 2015[46] China	Case-control Prospective	Mixed	20-37	73	3D ultrasound	After the 28th week global and regional brain volumes were progressively smaller in CHD relative to controls (p<0.05). The diagnostic category (P<0.001) was independently associated with smaller brain volumes in fetuses with CHD and the highest ratios occurred in cases of HLHS followed by aorta hypoplasia, TGA and TOF (P<0.001).
Sun *et al.* 2015[36] Canada	Case-control Prospective	Mixed	Mean±SD 36±1	24**	Phase contrast magnetic resonance and T2 mapping	13% reduction in brain volume (P<0.001) or a full 1-SD reduction in estimated brain weight Z score (P<0.001).
Schellen *et al.* 2015[23] Austria	Case-control Retrospective	TOF	Mean±SD: 25.7±3.6 (median 25.1) in	24	MRI	Mean TBV in fetuses with TOF was significantly lower than in normal control fetuses (difference of estimated means in TOF - controls = -13,874mm^3, P <0.001), with reduced GMV (difference of

			cases and 25.6±3.6 (median 25.0) in controls			estimated means in TOF - controls = -4242mm^3, P=0.003) and SBV (difference of estimated means in TOF - controls = -9633, P=0.001). Mean ICV was not significantly lower in cases (P=0.314). Mean VV was significantly higher (difference of estimated means in TOF - controls = 1962mm^3, P=0.005) in fetuses with TOF; the lateral ventricles were, on average, significantly wider than in normal control fetuses (narrower lateral ventricle width, P=0.012; wider lateral ventricle width, P=0.023). Compared with normal control fetuses, fetuses with TOF exhibited greater eCSFV (difference of estimated means in TOF - controls = 0.05, P <0.001) in relation to ICV.
Masollar *et al.* 2015*[35]† Spain	Case-control Prospective	Mixed	36-38	58	MRI	Fetuses with CHD showed significantly smaller brain, intracranial and opercular volumes than controls. CHD fetuses presented significantly decreased depths for left and right parieto-occipital, cingulate, and calcarine fissures compared with controls. Also observed a significantly increased depth of the left insular lobe with respect to controls. No differences were found in the right insula and Sylvian's fissure depth between the two groups.

** 3 fetuses with chromosomal abnormalities and 3 had associated abnormalities (excluded from this review); *† authors described the study as cohort, but includes controls (case-control); †† This study includes a subpopulation from the study by Limperopoulos et al. 2010; HLHS: hypoplastic left heart syndrome; TOF: Tetralogy of Fallot; TGA: transposition of the great arteries; SD: standard deviation; TBV: Total brain volume; GMV: Gray matter volume; SBV: subcortical brain volume; ICV: intracranial cavity volume; VV: ventricular volume; eCSFV: external cerebrospinal fluid volume; MRI: magnetic resonance imaging.

Table 3. Summary of the studies included which reported changes in brain metabolism/maturation in fetuses with Congenital Heart Defects (CHD).

Author, year and origin	Study Design Data collection	CHD diagnosis	Gestational age at assessment (weeks)	CHD assessed	Assessment method	Findings
Limperopoulos *et al.* 2010[21] USA/Canada	Case-control Prospective	Mixed[c]	Range 25-37 (median 30)	36	MRS	N-acetylaspartate (NAA)/choline ratios increased in CHD fetuses, but were slower to rise.
Sun *et al.* 2015[36] Canada	Case-control Prospective	Mixed	Mean±SD 36±1	24**	phase contrast magnetic resonance and T2 mapping	When the fetuses were compared to the controls, a mean 10% reduction in the oxygen saturation (SaO_2) of blood supplied to the developing brain was found. Because there was no difference in cerebral blood flow, this resulted in an almost statistically significant 15% reduction in cerebral oxygen delivery (DO_2). Due to no difference in the extraction of oxygen by the brain, the result was a mean 32% reduction in cerebral oxygen consumption (VO_2) in fetuses with CHD.
Masollar *et al.* 2015*[35]† Spain	Case-control Prospective	Mixed	36-38	48	MRS	Increased Inositol/Choline ratio in the frontal lobe and basal ganglia, decreased levels of NAA/Choline and Choline/Creatinine ratios also in both areas when compared with controls. A peak of lactate was identified in three CHD cases (one with critical aortic stenosis and hypoplastic left heart syndrome, one transposition of great vessels and one tricuspid atresia with hypoplastic right ventricle).

** 3 fetuses with chromosomal abnormalities and 3 had associated abnormalities (excluded from this review); *† authors described the study as a cohort study, but has controls as well (case-control); MRS: magnetic resonance spectroscopy; SD: standard deviation.

Table 4. Summary of the studies included which reported changes in brain blood flow in fetuses with Congenital Heart Defects (CHD).

Author, year and origin	Study Design Data collection	CHD diagnosis	Gestational age at assessment in weeks	CHD assessed	Assessment method	Findings
Jouannic *et al.* 2002[44] France	Case-control Prospective	TGA	36-38	23	Doppler ultrasound	The MCA PI in TGA was significantly lower than controls (median 1.37; range 1.10–2.02 vs 1.68; range 1.46–2.04, p<0.001). No significant difference in the PI in the UA, the aorta and the ductus venosus Doppler between fetuses with TGA and controls.
Donofrio *et al.* 2003[41] USA	Case-control Prospective	Mixed	20 weeks to delivery (mean±SD 26.5 ± 3.8)	36	Doppler ultrasound	Mean CPR was lower in fetuses with CHD compared to normal (mean±SD 1.09 ± 0.15 vs 1.16 ± 0.13, p<0.01), and mean cerebral artery RI was lower for fetuses with CHD compared to normal (0.79 ± 0.07 vs 0.84 ± 0.04, p<0.001). Mean umbilical artery RI was not different between the two groups (0.74 ± 0.10 vs 0.73 ± 0.07). Mean CPR in the subgroups according to the CHD diagnosis were: HLHS (1.05 ± 0.12, p<0.002), LVOTO (1.21 ± 0.20, p=NS), TGA (1.06 ± 0.08, p=0.07), TOF (1.11±0.19, p=NS), HRHS (1.09 ± 0.16, p=NS). The proportion of fetuses with abnormal CPR (< 1) were 5% (1) in normal fetuses compared to 44% (16) in fetuses with CHD (p<0.001), 58% in HLHS (7) (p<0.001), 0 in LVOTO (p=1), 25% (1) in TGA (p<0.30), 45% (5) in TOF (p<0.02), 60% (3) in HRHS (p<0.002). Mean MCA RI in the subgroups according to the CHD diagnosis were: HLHS (0.78 ± 0.07, p<0.001), LVOTO (0.80 ± 0.02, p=NS), TGA (0.80 ± 0.07, p<0.05), TOF (0.78 ± 0.07, p<0.001), HRHS (0.85 ± 0.07, p=NS). Mean UA RI in the subgroups according to the CHD diagnosis were: HLHS (0.75 ± 0.07, p=NS), LVOTO (0.67 ± 0.09, p=NS), TGA (0.75 ± 0.08, p=NS), TOF (0.73 ± 0.14, p=NS), HRHS (0.79 ± 0.08, p=NS).
Kaltman *et al.* 2005[43] USA	Case-control Cross-sectional	Mixed	20-39	58	Doppler ultrasound	Significant differences between z scores were seen in UA PI for right sided obstructive lesions (mean±SD 0.65±1.33 vs -0.14±1.11, p=0.045) and MCA PI for HLHS (-1.22±1.58 vs -0.12±1.50, p=0.009) when

						compared to controls. The U/C-PI ratio was not significantly different between groups (P=0.287).
Modena *et al.* 2006[42] USA	Case-control Prospective	Mixed	mid-second trimester	71	Doppler ultrasound	No significant differences were found, between the CHD and the gestational age-matched controls group) in the mean values for MCA PI (mean±SD 2.03±0.47 vs 2.08±0.43, p=0.518), UA PI (mean±SD 1.24±0.45 vs 1.16±0.29, p=0.246), z score (mean±SD 0.43±1.93 vs 0.64±1.76, p=0.515) and CPR (mean±SD 1.76±0.79 vs 2.14±2.24, p=0.199). All abnormal (<5th centile) MCA PI were in fetuses with intra cardiac mixing lesions (5/71 vs 0/71, p=0.023). No significant differences were found, between the CHD and the gestational age-matched controls group, in the CPR <5th centile (8/71 vs 2/71, p=0.049) or UA PI >95th centile (6/71 vs 3/71, p=0.251).
Chen *et al.* 2008[37] China	Case-control Prospective	Ebsteins	23-37	11	Doppler ultrasound	Significant differences between cases and controls were seen in UA PI (p<0.005), MCA PI (p<0.001) and MCAPI/UAPI (p<0.001)
Guorong *et al.* 2009[38] China	Case-control Prospective	Mixed	20-40	45	Doppler ultrasound	Significant differences between z scores of cases and controls were seen in UA PI (p=0.001) and UA PI/MCA PI (p<0.001). There was no significant difference in the MCA PI between fetuses with CHD (n = 45) and controls (n = 275), while fetuses with CHD complicated by congestive heart failure (n = 10) had a decreased MCA PI (p<0.001) compared to controls.
Berg *et al.* 2009[40] Germany	Case-control Retrospective	Mixed	19-41	113	Doppler ultrasound	Significant differences between z scores of cases and controls were seen for CPR (p<0.05). Differences were not significant for MCA PI or RI
Itsukaichi *et al.* 2011[39] Japan	Case-control Retrospective	Mixed	range 28-34 (median 30)	44	Doppler ultrasound	Statistically significant differences between cases and controls were seen in MCA RI <5th decile (25% vs 7.1%, p=0.0025) and <10th decile (p=0.0016), UA RI >90th decile (22.7% vs 3.6%, p=0.0003) and MCA RI/UA RI <1 (11.4% vs 0, p=0.0007). The percentages of fetuses showing MCA RI values <10th percentile (29.5% vs 8.6%, p=0.0016) and UA RI values >90th percentile were significantly higher in the CHD group than in the control group.
Yamamoto *et al.* 2013[48]	Case-control	mixed	third trimester	89	Doppler ultrasound	Lower MCA-PI, higher UA-PI and lower CPR were observed in HLHS and isolated coarctation with

Canada	Retrospective		(mean 32)			reversed arch flow (n = 6) (P < 0.001) but not TGA, POTO or isolated coarctation with antegrade arch flow (n = 15) compared with controls. No difference was found between HLHS with anatomical coarctation and those without.
Masollar *et al.* 2014[47] Spain	Case-control Prospective	mixed	median 22+3 (range 20+0-23+5)	95	Doppler ultrasound	Fetuses with CHD showed significantly lower MCA-PI and CPR Z-scores (-0.23 vs 0.34 and -0.37 vs 0.30, respectively; both P < 0.001) and higher FMBV Z-scores (2.35 vs 0.15; P < 0.001). FMBV > 95(th) percentile was observed in 81.1% of cases as compared with 10.5% in controls (P < 0.001).
Zeng *et al.* 2015[46] China	Case-control Prospective	Mixed	20-37	73	3D ultrasound	MCA PI was lower in cases compared to controls (mean±SD 1.66±0.42 vs 1.77±0.35 p=0.04).
Zeng *et al.* 2015[45] China	Case-control Prospective	Mixed	19+6-30+3 (cases) and 20+0 -30+7 (controls)	112	3D Power Doppler ultrasound	HLHS had significantly lower MCA-PI Z-scores than did the controls (mean±SD −2.01 ± 1.31 vs −0.63 ± 0.77, P< 0.001). The MCA-PI Z-score was lower in fetuses with LSOL than in controls, but this difference did not reach the level of statistical significance (−1.04 ± 1.14 vs −0.63 ± 0.77, p=0.32). The MCA-PI Z-score did not differ between fetuses with RSOL and TGA and controls (P=0.90 and P=0.99, respectively). Total intracranial blood flow perfusion and perfusion of the territories of the three main arteries were significantly increased in the fetuses with HLHS compared with normal controls (all P < 0.001). Fetuses with LSOL also had significantly higher 3D power Doppler values than did controls (all P < 0.001). The blood flow perfusion indices in the ACA territory were significantly higher in the fetuses with TGA than in the controls (all P < 0.01). There were no significant differences in 3D power Doppler indices between fetuses with RSOL and controls. In the fetuses with CHD, the increases in VI, FI and VFI relative to controls were highest in the ACA territory (P < 0.05).
Sun *et al.* 2015[36] Canada	Case-control Prospective	Mixed	mean±SD 36±1	24**	phase contrast magnetic resonance and T2	When the fetuses were compared to the control, a mean 10% reduction in the oxygen saturation (SaO2) of blood supplied to the developing brain was found. Because there was no difference in cerebral blood flow, this resulted in an almost statistically significant 15%

					mapping	reduction in cerebral oxygen delivery (DO2). Due to no difference in the extraction of oxygen by the brain, the result was a mean 32% reduction in cerebral oxygen consumption (VO2) in fetuses with CHD.
Masollar *et al.* 2015‡‡ *†[35] Spain	Case-control Prospective	mixed	20-24	58	Doppler ultrasound	Fetuses with CHD showed significantly lower MCA-PI and CPR mean Z-score values, and significantly higher frontal FMBV Z-score values compared with controls.

** 3 fetuses with chromosomal abnormalities and 3 had associated abnormalities (excluded from this review); ‡‡ study cohort might overlap with that of Masoller et al 2014; *† authors described the study as cohort, but has controls as well (case-control); TGA: transposition of the great arteries; MCA: middle cerebral artery; PI: pulsatility index; UA: umbilical artery; CPR: cerebroplacental ratio; RI: resistance index; HLHS: hypoplastic left heart syndrome; LVOTO: left ventricular outflow obstruction; TOF: Tetralogy of Fallot; HRHS: hypoplastic right heart syndrome; U/C: umbilical to cerebral ratio; POTO: pulmonary outflow tract obstruction; FMBV: LSOL: left-sided obstructive lesions; RSOL: right-sided obstructive lesions; fractional moving blood volume; VI: vascularization index; FI: flow index; VFI: vascularization flow index; ACA: anterior cerebral artery

Supplementary Table 1. Search strategy using Medline, Embase and The Cochrane Library (since inception) including The Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and The Cochrane Central Register of Controlled Trials (CENTRAL).

Databases**:** Embase®, Embase® Alert, MEDLINE®

Set#	Searched for	Results
S15	**s13 or s14**	**1719**
S14	((s1 or s2 or s3) and (s4 or s5 or s6) and (s7 or s8 or s9 or s10 or s11)) not (animal(yes) or EMB.EXACT("nonhuman"))	1537
S13	(s1 or s2 or s3) and (s4 or s5 or s6) and (s7 or s8 or s9 or s10 or s11) and human(yes)	1621
S12	(s1 or s2 or s3) and (s4 or s5 or s6) and (s7 or s8 or s9 or s10 or s11)	1811
S11	ti,ab(fetus[*2] or foetus[*2] or fetal[*2] or foetal[*2] or prenatal[*2] or "pre natal[*2]" or prepartal[*2] or "pre partal[*2]" or prepartum[*1] or "pre partum[*1]" or antenatal[*2] or "ante natal[*2]" or antepartal[*2] or "ante partal[*2]" or antepartum[*1] or "ante partum[*1]" or "in utero" or intrauterine or "intra uterine" or uterine or preimplant[*6] or "pre implant[*6]" or fetalis or foetalis or pregnan[*4] or trimester[*1])	1627149
S10	EMB.EXACT("fetomaternal transfusion") OR EMB.EXACT("intrauterine growth retardation") OR EMB.EXACT.EXPLODE("prenatal diagnosis") OR EMB.EXACT("prenatal development") OR EMB.EXACT("prenatal stress") OR EMB.EXACT("prenatal injury") OR EMB.EXACT("prenatal disorder") OR EMB.EXACT("prenatal period") OR EMB.EXACT("prenatal drug exposure") OR EMB.EXACT("prenatal exposure") OR EMB.EXACT("prenatal growth") OR EMB.EXACT("prenatal mortality") OR EMB.EXACT("prenatal screening") OR EMB.EXACT("prenatal care") OR EMB.EXACT.EXPLODE("pregnancy") OR EMB.EXACT.EXPLODE("multiple pregnancy") OR EMB.EXACT("prolonged pregnancy") OR EMB.EXACT("pregnancy complication") OR EMB.EXACT("high risk pregnancy") OR EMB.EXACT.EXPLODE("ectopic pregnancy") OR EMB.EXACT("pregnancy disorder") OR EMB.EXACT("pregnancy outcome") OR EMB.EXACT("pregnancy rate") OR EMB.EXACT("early pregnancy factor") OR EMB.EXACT("pregnant woman")	885654
S9	EMB.EXACT("fetus") OR EMB.EXACT("fetus outcome") OR EMB.EXACT.EXPLODE("fetus maturity") OR EMB.EXACT.EXPLODE("fetus	297644

	development") OR EMB.EXACT("fetus hypoxia") OR EMB.EXACT("fetus disease") OR EMB.EXACT("fetus distress") OR EMB.EXACT("fetus malformation") OR EMB.EXACT.EXPLODE("fetus function test") OR EMB.EXACT.EXPLODE("fetus echography") OR EMB.EXACT.EXPLODE("fetus control") OR EMB.EXACT("fetus heart rate") OR EMB.EXACT("fetus monitoring") OR EMB.EXACT("fetus blood") OR EMB.EXACT("fetus heart") OR EMB.EXACT.EXPLODE("fetus (anatomy)") OR EMB.EXACT("fetus circulation") OR EMB.EXACT("fetus growth") OR EMB.EXACT("fetus mortality") OR EMB.EXACT("fetus movement") OR EMB.EXACT("fetus resorption") OR EMB.EXACT("fetus death") OR EMB.EXACT("fetus wastage") OR EMB.EXACT("fetus risk") OR EMB.EXACT("fetus weight") OR EMB.EXACT("fetal hemorrhage") OR EMB.EXACT("fetotoxicity")	
S8	MESH.EXACT.EXPLODE("Prenatal Diagnosis") OR MESH.EXACT.EXPLODE("Ultrasonography, Prenatal") OR MESH.EXACT("Prenatal Exposure Delayed Effects") OR MESH.EXACT("Prenatal Injuries") OR MESH.EXACT("Prenatal Care") OR MESH.EXACT("Uterine Monitoring") OR MESH.EXACT("Pregnancy") OR MESH.EXACT("Pregnancy Complications") OR MESH.EXACT("Pregnancy Rate") OR MESH.EXACT.EXPLODE("Pregnancy Trimesters") OR MESH.EXACT("Pregnancy, High-Risk") OR MESH.EXACT.EXPLODE("Pregnancy, Multiple") OR MESH.EXACT("Pregnancy, Heterotopic") OR MESH.EXACT("Pregnancy, Prolonged") OR MESH.EXACT.EXPLODE("Pregnancy, Ectopic") OR MESH.EXACT("Pregnant Women") OR MESH.EXACT("Pregnancy, Unplanned") OR MESH.EXACT("Pregnancy, Unwanted")	715455
S7	MESH.EXACT.EXPLODE("Fetal Monitoring") OR MESH.EXACT.EXPLODE("Fetal Heart") OR MESH.EXACT.EXPLODE("Fetus") OR MESH.EXACT("Fetal Diseases") OR MESH.EXACT("Fetal Viability") OR MESH.EXACT("Fetal Movement") OR MESH.EXACT("Fetal Development") OR MESH.EXACT("Fetal Weight") OR MESH.EXACT("Fetal Organ Maturity") OR MESH.EXACT("Fetal Blood") OR MESH.EXACT("Fetal Death") OR MESH.EXACT("Fetal Resorption") OR MESH.EXACT("Fetal Distress") OR MESH.EXACT("Fetal Growth Retardation") OR MESH.EXACT("Fetal Hypoxia") OR MESH.EXACT("Fetal Mortality") OR MESH.EXACT("Heart Rate, Fetal") OR MESH.EXACT("Maternal-Fetal Exchange")	213787
S6	ti,ab((brain* or cranial or cerebral or cerebell* or craniocerebral or intracerebral or intracranial) near/5 (malform* or abnormal* or anomaly or anomalies or defect* or dysfunction* or develop[*5] or maturation* or maturity or impair* or delay* or function* or size or volume or growth or structur[*2] or microstructur[*2] or bleed* or microbleed* or hemorrhag* or microhemorrhag* or haemorrhag* or	721929

	microhaemorrhag* or impedance or damage* or injury or injuries or trauma*))	
S5	EMB.EXACT("brain malformation") OR EMB.EXACT("brain development") OR EMB.EXACT("nervous system development") OR EMB.EXACT("brain maturation") OR EMB.EXACT("brain dysfunction") OR EMB.EXACT("brain function") OR EMB.EXACT("brain size") OR EMB.EXACT("brain growth") OR EMB.EXACT.EXPLODE("brain metabolism") OR EMB.EXACT.EXPLODE("brain hemorrhage") OR EMB.EXACT("brain damage") OR EMB.EXACT("traumatic brain injury") OR EMB.EXACT("cerebellum injury") OR EMB.EXACT("brain injury")	372889
S4	MESH.EXACT.EXPLODE("Brain -- abnormalities") OR MESH.EXACT("Brain -- pathology") OR MESH.EXACT("Brain -- physiopathology") OR MESH.EXACT("Brain -- growth & development") OR MESH.EXACT("Brain Damage, Chronic") OR MESH.EXACT("Brain Injury, Chronic") OR MESH.EXACT("Brain Injuries") OR MESH.EXACT("Brain -- injuries") OR MESH.EXACT.EXPLODE("Cerebral Hemorrhage") OR MESH.EXACT("Intracranial Hemorrhages") OR MESH.EXACT("Intracranial Hemorrhage, Traumatic") OR MESH.EXACT.EXPLODE("Brain Hemorrhage, Traumatic") OR MESH.EXACT.EXPLODE("Subarachnoid Hemorrhage")	223671
S3	ti,ab(congenital* near/3 (heart or cardiac)) or ti,ab((heart or cardiac) near/3 defect*) or ti,ab((heart or cardiac) near/3 abnormalit*) or ti,ab((heart or cardiac) near/3 malform*) or ti,ab((heart or cardiac) near/3 (anomaly or anomalies)) or ti,ab((aortic or aorta) near/3 coarct*) or ti,ab(transpos[*6] near/3 (arteries or artery or vessel[*1])) or ti,ab(double near/3 outlet near/3 ventricle[*1]) or ti,ab(heart near/3 hypoplas*) or ti,ab((septal or septum) near/3 defect*) or ti,ab(paten[*2] near/3 ductus near/3 arteriosus) or ti,ab(fallot[*1] near/3 (tetralogy or trilogy)) or ti,ab(cyanotic near/3 (heart or cardiac))	209511
S2	EMB.EXACT.EXPLODE("congenital heart malformation") OR EMB.EXACT.EXPLODE("congenital heart disease") OR EMB.EXACT.EXPLODE("heart disease -- congenital disorder") OR EMB.EXACT("aorta coarctation") OR EMB.EXACT.EXPLODE("great vessels transposition")	162526
S1	MESH.EXACT.EXPLODE("Heart Defects, Congenital") OR MESH.EXACT.EXPLODE("Heart Diseases -- congenital")	124348

Databases:

- The Cochrane Database of Systematic Reviews (CDSR, Cochrane Reviews: Issue 11 of 12, November 2014) (2 references)
- Database of Abstracts of Reviews of Effects (DARE, Other Reviews: Issue 4 of 4, October 2014) (0 references)
- The Cochrane Central Register of Controlled Trials (CENTRAL, Trials: Issue 10 of 12, October 2014) (16 references)
- Health Technology Assessment Database (HTA, Technology Assessments: Issue 4 of 4, October 2014) (0 references)
- NHS Economic Evaluation Database (NHS-EED, Economic Evaluations: Issue 4 of 4, October 2014) (0 references)

ID	Search	Hits
#1	MeSH descriptor: [Heart Defects, Congenital] explode all trees	1541
#2	MeSH descriptor: [Heart Diseases] explode all trees and with qualifiers: [Congenital - CN]	22
#3	(congenital* near/3 (heart or cardiac)):ti,ab,kw	880
#4	((heart or cardiac) near/3 defect*):ti,ab,kw	842
#5	((heart or cardiac) near/3 abnormalit*):ti,ab,kw	233
#6	((heart or cardiac) near/3 malform*):ti,ab,kw	33
#7	((heart or cardiac) near/3 (anomaly or anomalies)):ti,ab,kw	29
#8	((aortic or aorta) near/3 coarct*):ti,ab,kw	55
#9	(transpos* near/3 (arteries or artery or vessel*)):ti,ab,kw	67
#10	(double near/3 outlet near/3 ventricle*):ti,ab,kw	7
#11	(heart near/3 hypoplas*):ti,ab,kw	57
#12	((septal or septum) near/3 defect*):ti,ab,kw	333
#13	(paten* near/3 ductus near/3 arteriosus):ti,ab,kw	494
#14	(fallot* near/3 (tetralogy or trilogy)):ti,ab,kw	105
#15	(cyanotic near/3 (heart or cardiac)):ti,ab,kw	52
#16	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15	2502

#17	MeSH descriptor: [Brain] explode all trees and with qualifiers: [Abnormalities - AB]	24
#18	MeSH descriptor: [Brain] this term only and with qualifiers: [Pathology - PA]	642
#19	MeSH descriptor: [Brain] this term only and with qualifiers: [Physiopathology - PP]	654
#20	MeSH descriptor: [Brain] this term only and with qualifiers: [Growth & development - GD]	65
#21	MeSH descriptor: [Brain Damage, Chronic] this term only	240
#22	MeSH descriptor: [Brain Injury, Chronic] this term only	26
#23	MeSH descriptor: [Brain Injuries] this term only	997
#24	MeSH descriptor: [Cerebral Hemorrhage] explode all trees	684
#25	MeSH descriptor: [Intracranial Hemorrhages] this term only	158
#26	MeSH descriptor: [Intracranial Hemorrhage, Traumatic] this term only	13
#27	MeSH descriptor: [Brain Hemorrhage, Traumatic] explode all trees	9
#28	MeSH descriptor: [Subarachnoid Hemorrhage] explode all trees	454
#29	((brain* or cranial or cerebral or cerebell* or craniocerebral or intracerebral or intracranial) near/5 (malform* or abnormal* or anomaly or anomalies or defect* or dysfunction* or develop* or maturation* or maturity or impair* or delay* or function* or size or volume or growth or structur* or microstructur* or bleed* or microbleed* or hemorrhag* or microhemorrhag* or haemorrhag* or microhaemorrhag* or impedance or damage* or injury or injuries or trauma*)):ti,ab,kw	10382
#30	#17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29	11446
#31	#16 and #30	159
#32	MeSH descriptor: [Fetal Monitoring] explode all trees	357
#33	MeSH descriptor: [Fetal Heart] explode all trees	115
#34	MeSH descriptor: [Fetus] explode all trees	1520
#35	MeSH descriptor: [Fetal Diseases] this term only	177
#36	MeSH descriptor: [Fetal Viability] this term only	7

#37	MeSH descriptor: [Fetal Movement] this term only	62
#38	MeSH descriptor: [Fetal Development] this term only	61
#39	MeSH descriptor: [Fetal Weight] this term only	18
#40	MeSH descriptor: [Fetal Organ Maturity] this term only	42
#41	MeSH descriptor: [Fetal Blood] this term only	543
#42	MeSH descriptor: [Fetal Death] this term only	208
#43	MeSH descriptor: [Fetal Resorption] this term only	1
#44	MeSH descriptor: [Fetal Distress] this term only	128
#45	MeSH descriptor: [Fetal Growth Retardation] this term only	273
#46	MeSH descriptor: [Fetal Hypoxia] this term only	26
#47	MeSH descriptor: [Fetal Mortality] this term only	6
#48	MeSH descriptor: [Heart Rate, Fetal] this term only	317
#49	MeSH descriptor: [Maternal-Fetal Exchange] this term only	314
#50	MeSH descriptor: [Prenatal Diagnosis] explode all trees	936
#51	MeSH descriptor: [Ultrasonography, Prenatal] explode all trees	494
#52	MeSH descriptor: [Prenatal Exposure Delayed Effects] this term only	252
#53	MeSH descriptor: [Prenatal Injuries] this term only	1
#54	MeSH descriptor: [Prenatal Care] this term only	1062
#55	MeSH descriptor: [Uterine Monitoring] this term only	17
#56	MeSH descriptor: [Pregnancy] this term only	63
#57	MeSH descriptor: [Pregnancy Complications] this term only	1161
#58	MeSH descriptor: [Pregnancy Rate] this term only	1143
#59	MeSH descriptor: [Pregnancy Trimesters] explode all trees	1473
#60	MeSH descriptor: [Pregnancy, High-Risk] this term only	188
#61	MeSH descriptor: [Pregnancy, Multiple] explode all trees	204

#62	MeSH descriptor: [Pregnancy, Heterotopic] this term only	0
#63	MeSH descriptor: [Pregnancy, Prolonged] this term only	113
#64	MeSH descriptor: [Pregnancy, Ectopic] explode all trees	172
#65	MeSH descriptor: [Pregnant Women] this term only	97
#66	MeSH descriptor: [Pregnancy, Unplanned] this term only	56
#67	MeSH descriptor: [Pregnancy, Unwanted] this term only	43
#68	(fetus* or foetus* or fetal* or foetal* or prenatal* or "pre natal*" or prepartal* or "pre partal*" or prepartum* or "pre partum*" or antenatal* or "ante natal*" or antepartal* or "ante partal*" or antepartum* or "ante partum*" or "in utero" or intrauterine or "intra uterine" or uterine or preimplant* or "pre implant*" or fetalis or foetalis or pregnan* or trimester*):ti,ab,kw	34596
#69	#32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68	34773
#83	**#16 and #30 and #69**	**18**

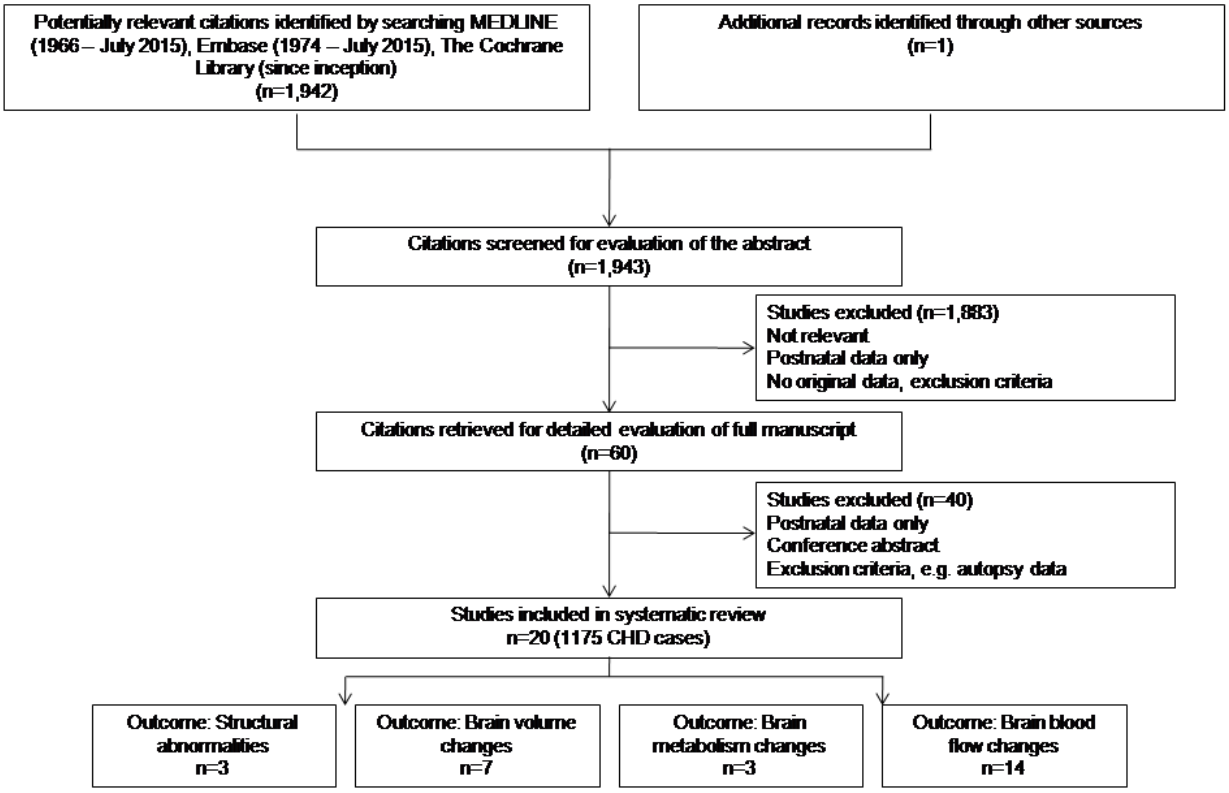

Figure 1

Figure 1. Flow of study identification. CHD = congenital heart defects.

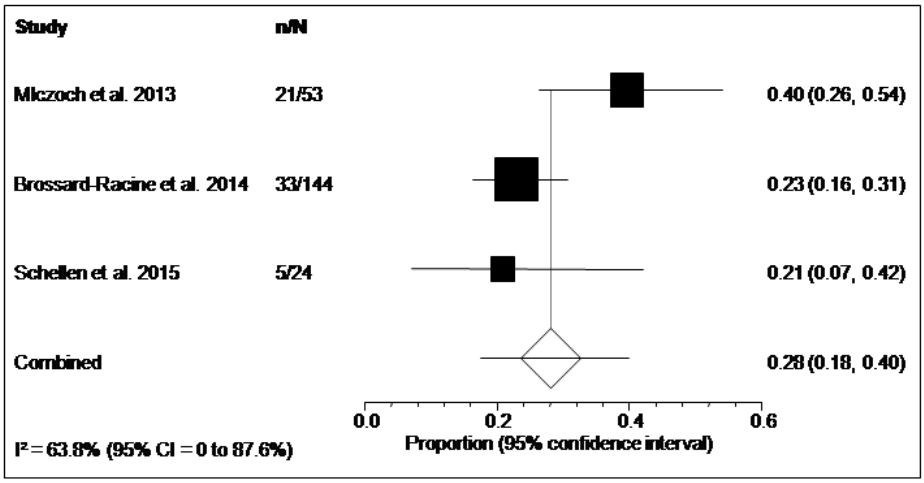

Figure 2

Figure 2. Pooled prevalence (forest plot) of structural brain abnormalities in fetuses with congenital heart defects.

Each study is represented by a line. The box in the middle of the line represents the point effect estimate of this particular study. The midpoint of the box represents the point effect estimate, that is, the mean effect estimate for each study. The area of the box represents the weight given to the study. The diamond below the studies represents the overall estimate. The width of the line shows the confidence interval (CI) of the effect estimate of individual studies. The width of the diamond shows the CI for the overall effect estimate. N = total number in group, while n = number in group with the outcome. Heterogeneity (I^2) = diversity between studies.

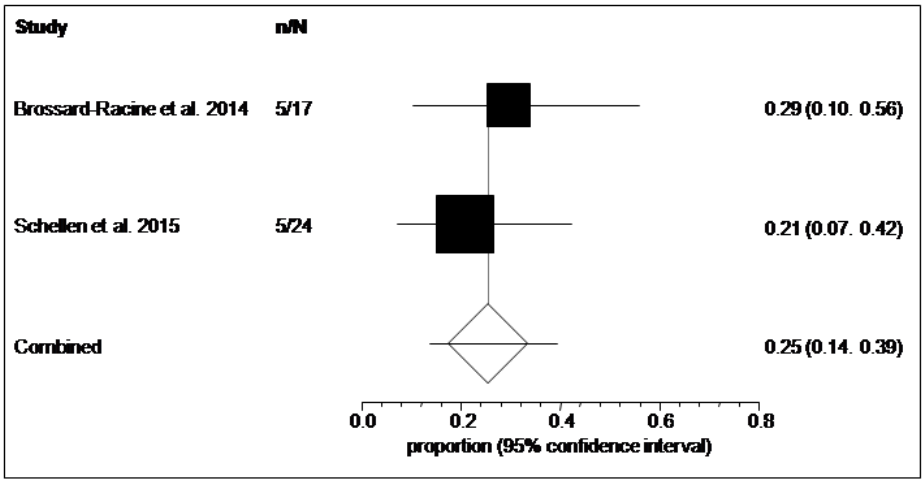

Figure 3

Figure 3. Pooled prevalence (forest plot) of structural brain abnormalities in fetuses with Tetralogy of Fallot.

Each study is represented by a line. The box in the middle of the line represents the point effect estimate of this particular study. The midpoint of the box represents the point effect estimate, that is, the mean effect estimate for each study. The area of the box represents the weight given to the study. The diamond below the studies represents the overall estimate. The width of the line shows the confidence interval (CI) of the effect estimate of individual studies. The width of the diamond shows the CI for the overall effect estimate. N = total number in group, while n = number in group with the outcome. Heterogeneity (I^2) = diversity between studies.

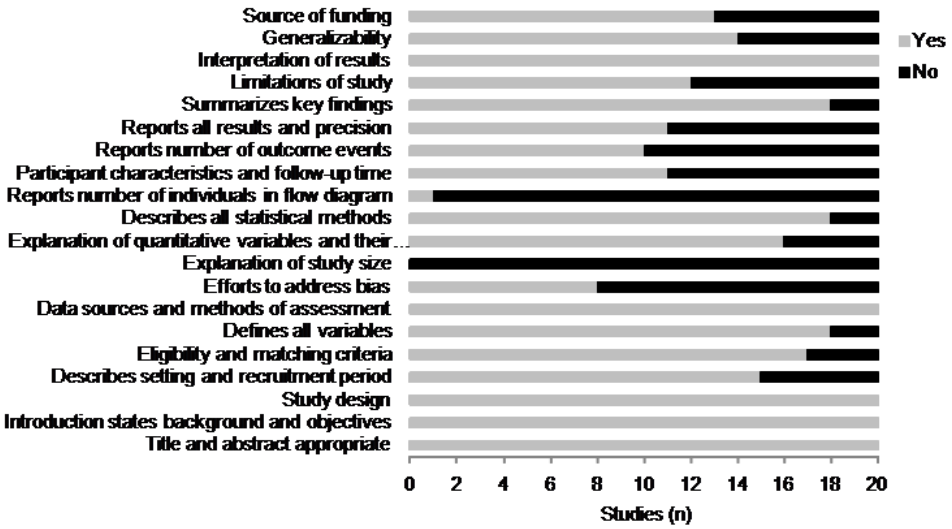

Figure 4

Figure 4. Quality criteria of the included articles, as assessed using the Strengthening the Reporting of Observational Studies in Epidemiology checklist.