The placenta in fetal congenital heart disease

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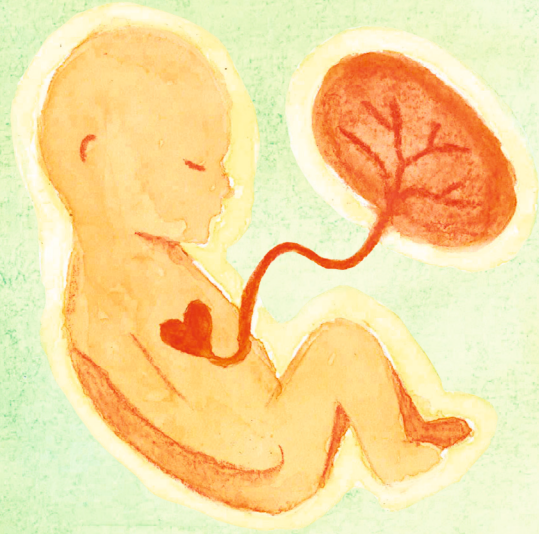

CHAPTER 2

Placenta morphology and biomarkers in pregnancies with congenital heart disease – a systematic review

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ABSTRACT

Impaired placentation is an important contributing factor to intra-uterine growth restriction and pre-eclampsia in fetuses with congenital heart defects (CHD). These pregnancy complications occur more frequently in pregnancies with fetal CHD. One of the most important factors influencing the life of children with CHD is neurodevelopmental delay, which seems to start already in utero. Delayed neurodevelopment in utero may be correlated or even (partly) explained by impaired placentation in CHD cases. This systematic review provides an overview of published literature on placental development in pregnancies with fetal CHD. A systematic search was performed and the Newcastle-Ottawa scale was used to access data quality. Primary outcomes were placenta size and weight, vascular and villous architecture, immunohistochemistry, angiogenic biomarkers and/or placental gene expression. A total of 1161 articles were reviewed and 21 studies were included. Studies including CHD with a genetic disorder or syndrome and/or multiple pregnancies were excluded. Lower placental weight and elevated rates of abnormal umbilical cord insertions were found in CHD. Cases with CHD more frequently showed microscopic placental abnormalities (i.e. abnormal villous maturation and increased maternal vascular malperfusion lesions), reduced levels of angiogenic biomarkers and increased levels of anti-angiogenic biomarkers in maternal serum and umbilical cord blood. Altered gene expression involved in placental development and fetal growth were found in maternal serum and CHD placentas. In conclusion, abnormal placentation is found in CHD. More extensive studies are needed to elucidate the contribution of impaired placentation to delayed neurodevelopment in CHD cases.

INTRODUCTION

With an incidence of five to eight per thousand newborns, congenital heart defects (CHD) are the most common congenital anomalies [1]. As approximately half of the CHDs are severe and treatment carries risks, CHDs are a large contributor to infant mortality worldwide [1,2]. Due to continuous improvement of ICU-care and cardiothoracic surgery, together with increased prenatal detection, survival rates of affected newborns have increased greatly. For that reason, the focus of innovation has shifted from increasing survival rates to improvement of long-term (neuro)developmental outcomes [1-3].

An important part of the morbidity in children and adolescents with CHD is neurodevelopmental delay, which is reported in a significant amount of cases [4-9]. In earlier literature, this impairment was attributed to the adverse effects of complex cardiothoracic surgery in early life [4-6,8,9]. More recently, a decreased prenatal and postnatal head circumference and delayed cortical maturation on prenatal ultrasound and MRI were found in CHD fetuses and newborns before surgery [5-9]. This raises the question whether the hemodynamic effects of the CHD induce intrauterine exposure to decreased flow or low saturation in early neonatal life.

A second finding in pregnancies with fetal CHD is the increased incidence of intra-uterine growth restriction (IUGR), pre-eclampsia (PE) and pregnancy induced hypertension (PIH) [10-22]. These signs of impaired placental development are confirmed by an increased umbilical artery resistance and decreased global placental perfusion in fetuses with CHD [18-27]. The increased incidence of placental pathology in pregnancies with CHD, raises the question if this is a possible contributor to impaired neurodevelopment in these fetuses, as increased umbilical artery resistance in fetuses with CHD is associated with altered (neurodevelopmental) outcomes [24-25]. The relation between placenta characteristics, placental function and fetal neurodevelopment has not yet been studied in CHD cases and is still hypothetical.

In this systematic review, an overview of the literature on isolated CHD and placenta development is provided, aiming to explore the role of the placenta in the relation to CHD and fetal neurodevelopment.

MATERIALS AND METHODS

Search strategy

A systematic search was performed in Pubmed, Embase, Web of Science, Cochrane and Emcare on April 15th 2021. The search terms contained “congenital heart defect”, “placenta”, “genetics”, “fetus”, “neurodevelopment”, “outcome”, “long term outcome”, “angiogenic”, “biomarker”. Publications from all dates were included. The complete search string is available in appendix A.

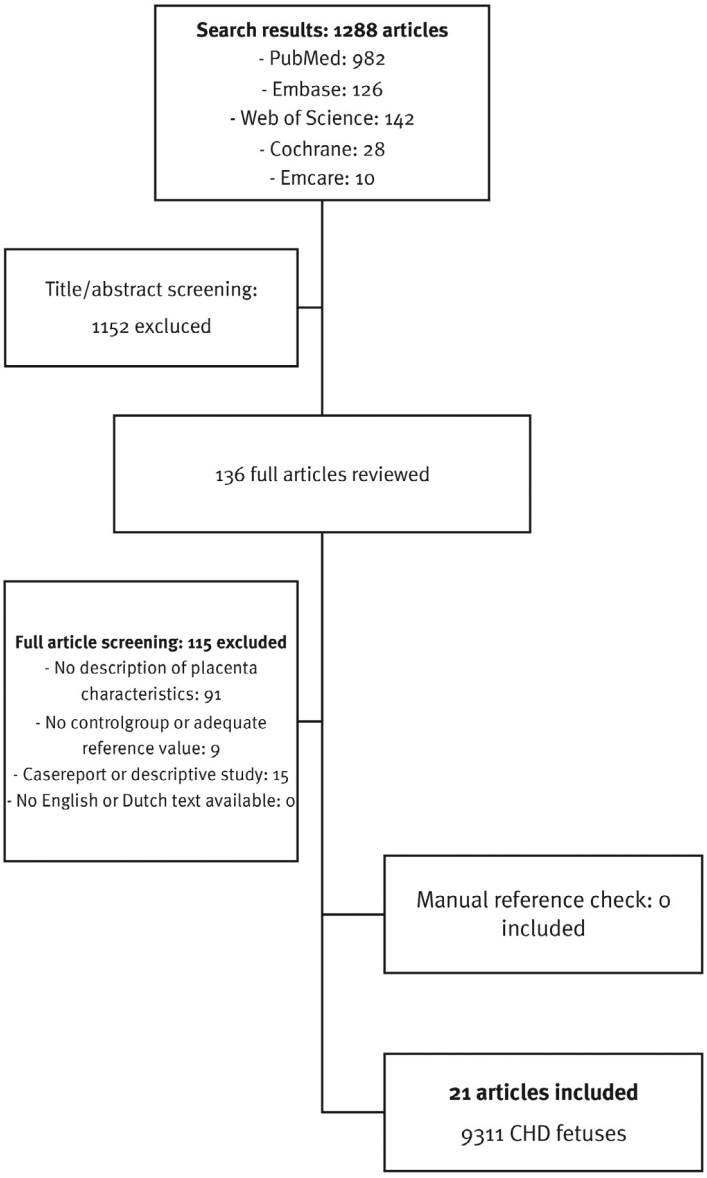

Figure 1a: Flowchart of included studies

Study selection

The screening of the title/abstract and subsequently the reading of the full-text articles was performed by two independent researchers (MS, MA). A third researcher (MH) was consulted when agreement was not reached. Studies were eligible for inclusion if 1) newborns with isolated congenital heart disease were included; and 2) placenta characteristics regarding macroscopic measurements, immunohistochemistry, vascular

and villous architecture, immunoreactivity, angiogenic biomarkers and/or placenta genetics were provided and; 3) a control group or a comparison with reference values for the described placenta characteristics was present. As the presence of a genetic syndrome or multiple pregnancies have effect on intra-uterine growth and developmental outcomes [28,29], studies on congenital heart disease with a genetic disorder or syndrome and/or multiple pregnancies were excluded, in order to identify the sole effect of the congenital heart disease. Studies with less than ten cases were also excluded from the review. Cross-referencing was performed manually on the included studies.

Quality assessment and data extraction

Data quality was assessed using the Newcastle Ottawa Scale (NOS) for assessing the quality of non-randomized studies [30].

Patient characteristics and placenta characteristics regarding macroscopic measurements, immunohistochemistry, vascular and villous architecture, immunoreactivity, angiogenic biomarkers and/or placenta genetics were extracted and analyzed.

RESULTS

Study selection

The conducted search generated 1288 articles. After screening on title/abstract, 136 articles were read full text and 21 articles were included (Figure 1) [31-51]. No relevant studies were found by cross-referencing. Study characteristics are shown in Table 1.

Study groups were not always comparable for the different included studies and differed specifically on categorization of types of CHDs (Table 1). Most studies included all CHD, whilst others only included 'major' CHD (defined as CHD requiring cardiac intervention within the first year of life) or included only one specific congenital heart defect.

Of the included studies, 10 studies describe macroscopic placenta characteristics, 6 studies describe microscopic placenta characteristics, 4 studies describe angiogenic biomarkers in maternal and/or umbilical cord serum and 7 studies describe genetic expression in maternal serum and/or placental tissue.

Quality assessment

Quality assessment is shown in Supplement 1. Most included studies in this systematic review were rated with an adequate quality. According to the NOS quality assessment, 16 articles obtained five or more out of six stars. One study obtained only one star, due to inadequate representativeness of the cohort and inadequate selection of the controls. Three studies obtained three stars, as they had no control group and compared the measurements with reference values.

Table 1: Overview of included studies

	Study design	Single- or multi-center	Number of patients	Number of controls	Type of CHD	Time of measurement	Outcome measure(s)
Arcelli (2010), Italy	Retrospective case-control	S	40	48	All CHD	Second trimester; Postpartum	mRNA species in maternal serum; gene expression in placental tissue
Llurba (2013), Spain	Prospective case-control	S	68	340	Major congenital cardiac defects	First trimester	PlGF and PAPP-A in maternal serum
Andescavage (2014), USA	Prospective case-control	S	41	94	All CHD	Second and third trimester	Placental volume (fetal MRI)
Llurba (2014), Spain	Prospective case-control	S	65	204	Major congenital cardiac defects	Second trimester; Postpartum	PlGF, sFlt-1, sEng in maternal blood; PlGF, sFlt-1, sEng in umbilical cord blood
Curti (2015), Italy	Prospective case-control	S	10	50	All CHD	Third trimester	PlGF in maternal blood
Jones (2015), USA	Retrospective case-control	M	16	18	HLHS	Postpartum	Placenta weight, umbilical cord insertion, parenchymal morphology of the placenta
Albalawi (2016), USA	Retrospective case-control	S	200	200	CHD requiring cardiac surgery within 6 months	Postpartum	Placental cord insertion, placenta-to-birth weight ratio
Curti (2016), Italy	Prospective case-control	S	39	31	All CHD	Second trimester	mRNA species in maternal serum
Matthiesen (2016), Denmark	Retrospective cohort	M	7,569	916,853	All CHD	Postpartum	Placenta weight
Contro (2017), Italy	Retrospective case-control	S	36	42	CNTRA, LVOT	Second trimester	Gene expression (MAPK1, IQCAP1, Visfafin) in maternal serum
Fantasia (2018), UK	Prospective cohort	S	196	49,898	Major congenital cardiac defects	First trimester	PlGF and PAPP-A in maternal serum
Morano (2018), Italy	Retrospective case-control	M	10	30	VSD	Second trimester	mRNA Tenascin-X gene in maternal serum

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Table 1: *[continued]*

	Study design	Single- or multi-center	Number of patients	Number of controls	Type of CHD	Time of measurement	Outcome measure(s)
Rychik (2018), USA	Prospective cohort	S	120	No controls*	Complex CHD	Postpartum	Placenta weight, placenta-to-birth weight ratio, placenta pathology
Takemoto (2018), Japan	Prospective case-control	S	37	626	All CHD	Postpartum	Placenta-to-birth weight ratio
Miremberg (2019), Israel	Retrospective case-control	S	32	34	Severe CHD with termination of pregnancy	Postpartum	Placenta weight, placenta-to-birth weight ratio, maternal and fetal vascular malperfusion lesions of the placenta, inflammatory lesions of the placenta, umbilical cord abnormalities
Radhakrishna (2019), USA	Prospective case-control	S	8	10	VSD	Postpartum	Gene expression in placental tissue
Russell (2019), USA	Prospective cohort	S	133	No controls*	CHD requiring surgery in infancy	Postpartum	PRA genes damaging variants in placental tissue
Schlatterer (2019), USA	Prospective cohort	S	51	No controls*	All CHD	Postpartum	Placenta weight, placenta-to-birth weight ratio, placenta pathology
Courtney (2020), USA	Retrospective case-control	S	24	18	HLHS, TGA	Postpartum	Gene expression in placenta tissue Placenta-to-birthweight ratio, parenchymal morphology of the placenta
Giorgione (2020), Italy	Retrospective case-control	S	480	456	Major congenital cardiac defects	Postpartum	Placenta disorders (placenta praevia, placental abruption, placenta accrete/ increta/percreta, cord insertion abnormalities)
Ozcan (2021), USA	Retrospective cohort study	S	47	92	Major congenital cardiac defects	Postpartum	Placenta weight, placenta-to-birthweight, placenta perfusion defects

**Compared to population reference values*

Study results

Macroscopic placenta characteristics

Placental weight

In Tetralogy of Fallot (ToF), double-outlet right ventricle (double-outlet RV), major ventricular septal defects (VSDs) [39] and hypoplastic left heart syndrome (HLHS), a reduced absolute placental weight and placenta weight percentiles were found at birth (Table 1) [36]. Placenta volumes measured by MRI between 18 and 39 weeks of gestation, tended to be smaller in a study with mixed CHD cases, but the found differences did not reach statistical significance [33].

As placenta weight does not differentiate between cases with and without IUGR, it is important to identify placenta weight in relation to the birthweight. Five studies reported on placenta-to-birthweight ratio's, a measure to assess placental weight by correcting for birthweight, and described conflicting results. Four studies, of which three with a retrospective design, found no significant difference in placenta-to-birthweight ratio in CHD cases [37,44,45,51], suggesting that smaller placentas in CHD are only present in cases with a low birthweight. Three prospective studies did find a significant lower placenta-to-birthweight ratio in CHD cases [43,48,49], which means that the placentas were even smaller than expected, based on the birthweight of these cases. If CHD placentas are smaller in comparison to birthweight, fetus were able to reach their growth potential, indicating preservation of the placental function.

Umbilical cord insertion

Abnormal umbilical cord insertion is associated with adverse pregnancy outcomes, such as IUGR and intra-uterine demise [52]. Significant elevated rates of abnormal umbilical cord insertion (marginal and velamentous insertions) were found in one study including 200 CHD cases [37]. No elevated rates of abnormal umbilical cord insertions were found in two smaller studies in 16 HLHS cases [31] and 32 cases with different types of CHD (HLHS, transposition of the great arteries, atrioventricular canal defect, ToF, double-outlet RV and coarctation of the aorta) [45], presumably because of the small number of inclusions. In major CHD cases, 4.5% had 'placental disorders' other than macroscopic morphology (defined as placenta praevia, placental abruption, abnormally invasive placenta), compared to 3.3% in healthy controls ($p = 0.046$) [50].

Microscopic placenta characteristics

Histological findings indicating impaired fetal-maternal exchange are more frequently found in pregnancies with CHD. It was first reported in HLHS cases, where fibrin deposition, distal villous hypoplasia, lower vascular area and lower vasculo-syncytial membrane counts were described [36,49]. Later this was confirmed in placentas of a group of mixed CHD cases, as fetal placental thrombosis, placental infarction, choriangiosis, infarction and delayed villous maturation were frequently reported, whilst these are

phenomena that are not found in placentas of healthy newborns [43,45,48,51]. There was no significant difference in incidence of microscopic placenta abnormalities in cases with and without PE, PIH and IUGR [48].

Angiogenic biomarkers

Angiogenic biomarkers in pregnancy, such as Placental Growth Factor (PlGF) and pregnancy-associated plasma protein A (PAPP-A) are mainly produced in the placental trophoblasts [53,54]. Altered expression of angiogenic biomarkers in CHD cases may modify vascular pathways in the placenta, as concentrations of the angiogenic biomarkers Placental Growth Factor (PlGF) and pregnancy-associated plasma protein A (PAPP-A) were significantly lower in maternal serum of CHD cases [32,34,38,41]. Soluble fms-like tyrosine kinase (sFlt-1) and soluble endoglin (sEng) are *anti*-angiogenic biomarkers and were significantly higher in maternal serum of CHD cases [34]. sFlt-1 and sEng levels were higher in umbilical cord blood of CHD cases [34]. None of the studies describing angiogenic biomarkers corrected for placenta weight. Alterations in expression of these (anti-) angiogenic biomarkers suggest placental dysfunction and impaired placental perfusion. These findings may explain the decreased birthweight and placenta weight in isolated CHD cases [41].

Genetic expression in the placenta

Altered expression of (m)RNA and alterations in genes associated with cardiac function and development were found in both placental tissue and maternal serum of CHD cases. A significant part of the described genes with altered expression are expressed in both placental tissue and other (fetal) organs. Most of the described proteins have intracellular or direct extracellular effects, though altered expression is found in both placenta tissue and maternal serum. Altered expression of genes associated with trophoblast development, placental development and fetal growth was also described (Table 2), demonstrating a presumable relation between CHD, placenta genetic expression and placental function [31,35,40,42,46,49]. Damaging variants in genes with positive regulation of angiogenesis (PRA) were found, suggesting an altered angiogenic pathway in placentas of CHD cases [47].

DISCUSSION

This systematic review found that CHD is associated with lower placental weight, placental abnormalities that suggest impaired placentation and altered genic expression in placental tissue. Similar characteristics are observed in placentas of IUGR, PE and PIH cases, all finding their origin in abnormal trophoblast invasion and placental insufficiency [55-66] . This suggests a relation between CHD and impaired placentation and possibly a decreased fetal-maternal exchange of oxygens and nutrients as a result of this in these cases. Remarkably, even in absence of PE and IUGR, characteristics of altered placentation and placental insufficiency are found in CHD cases.

Table 2. Overview of described aberrant genes

Study	Location	Type of CHD	Results	Aberrant genes	Clinical associations
Arcelli (2010)	Maternal serum, placental tissue	All CHD	mRNA expression	ACTN4; COLIA 2, FBLN1, HPSE, JARIDIB, P4HA2, PAPP-A; ET3, MYL7; FSCN1; MAP4; RAB36; SAVI, TNXB, TXN.	Contractile activity Extracellular matrix biosynthesis Congestive heart failure Contractile activity Contractile dysfunction Rhabdomyoma / aetiopathogenesis Morphogenesis
Curti (2016)	Maternal serum	All CHD	mRNA expression	FALZ; PAPP-A; PRKACB; SAV1; STK4; TNXB2.	Brain development Placental function Pattern formation and morphogenesis Tumor suppressor Trophoblast differentiation Heart rhythm disorders and connective tissue disease
Contro (2017)	Maternal serum	CNTRA, LVOT	mRNA expression	MAPK1; IQGAP1, Visfatin.	Trophoblast development Cardiomyocyte hypertrophy activation
Morano (2018)	Maternal serum	VSD	mRNA expression	Tenascin-X (TNXB)	Cardiac development (coronary vasculogenesis, valve development), collagen production
Radhakrishna (2019)	Placental tissue	VSD	DNA methylation	HEY2; ISL1; ACTC1; BMP4, TGFB1, PDGFRA, TBX2, EGR1, CXCR4, TLX3, DPP6, FGFR1.	Cardiac development Cardiac septum formation Cardiac muscle development Heart development, cardiac anomalies
Russell (2019)	Placental tissue	CHD requiring surgery in infancy	Frequency of damaging PRAs	117 damaging PRA variants	Positive regulation of angiogenesis
Courtney (2020)	Placental tissue	HLHS, TGA	RNA expression	393 genes, a.o. IGF2; CITED2; GLUT1, GLUT3, SNAT2.	Placental development, cardiac function Placental capillary patterning, body axis IUGR

A possible origin of these findings could be directed to altered protein and RNA expression of genes that are likewise involved in the origin of the CHD. These alterations may be responsible for the placenta pathological changes that party overlap the phenotype of classic placenta dysfunction based on insufficient trophoblast invasion.

Altered molecular expression in vascular developmental pathways impacts vascular development in both the placenta and fetal organs. Changes in protein expression of genes with a local effect on cardiac or placental tissue, as well as changed expression of proteins with a more distant effect were described in placental tissue and maternal serum. These findings advocate an effect on vascular developmental pathways in other fetal organs, in addition to the effect on placental and cardiac tissue. The origin of CHD is multifactorial and both environmental factors and genetic predisposition play an important role in this development [67]. One can hypothesize that angiogenic imbalance and altered vascular formation in the placenta of CHD cases may be due to epigenetic influences from vascular and circulatory alterations or due to hypoxic stress in early embryogenesis of CHD cases [43,49,68]. The hemodynamic effects of the CHD may cause epigenetic changes, resulting in altered vascular developmental pathways. This may result in angiogenic alterations, placental abnormalities and its associated diseases, nonetheless this hypothesis can also be the other way around. Factors contributing to the pathogenesis of the CHD appear to also effect the development of the placenta and influence epigenetics of placental tissue, as common genetic contributors are found [47,49,69]. Similarly, the described altered levels of angiogenic biomarkers could be related to placenta size, as lower placental weight is common in CHD cases. Future studies on angiogenic biomarkers in placental tissue should index for placental weight, to get a better understanding of the effect of these biomarkers in the developmental pathway of CHD, angiogenic factors and placentation.

The next step in this hypothesis is the idea that delayed fetal brain maturation and delayed neurodevelopment at child age are caused by the same vascular alterations, as the placental changes are also found in CHD cases without PE and IUGR [7,8]. The process of impaired placenta perfusion, altered vascular genetic pathways and altered angiogenic expression is presumably comparable in CHD cases and cases of PE and IUGR, as these findings were also found in the absence of these diseases in CHD cases. Impaired placenta function and altered vascular expression in the placenta can cause impaired fetal organ perfusion and hypoxia.

Hypoxia and reduced organ perfusion may specifically contribute to delayed development of the brain, as this organ is extremely sensitive to hypoxia [70,71]. This effect is demonstrated in fetuses with CHD, as reduced cerebral oxygenation and impaired brain growth on MRI was found in these fetuses [72] and dysregulation of the angiogenesis was found in cerebral tissue of fetal CHD cases [73]. In addition, more postnatal brain injuries (white matter injury, intraparenchymal hemorrhage, intraventricular hemorrhage,

subdural hemorrhage) within the first five days of life were found in CHD cases with abnormal placenta pathology [48]. Moreover, this hypothesis is supported by the findings in a fetal sheep model, in which placental hypoxia levels similar to hypoxia in CHD cases were imitated. In brain tissue of these sheep, microglial morphology was altered, indicating an effect of hypoxia on brain pathology. [74] An altered angiogenic environment could furthermore contribute to hypoxic stress and impaired microvascular development of the brain. This may therefore contribute to the impaired neurodevelopment and delayed brain maturation in CHD fetus.

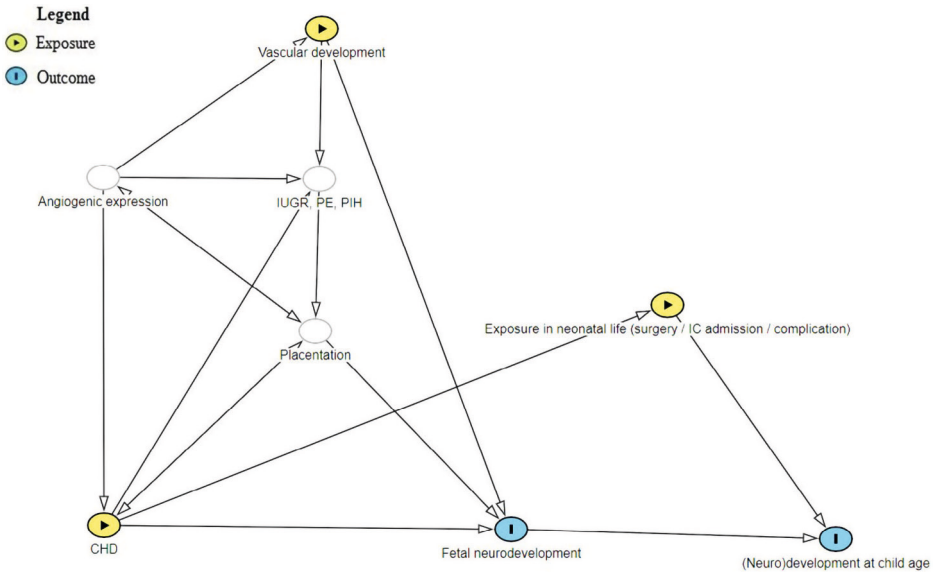

Figure 2: The directed acyclic graph of hypothetical associating factors, available on www.dagitty.net.
The directed acyclic graph of hypothetical associating factors demonstrates the complex causal pathway of CHD, angiogenic factors, placentation and neurodevelopment and the relation between the different associating factors

In this review, placental function is assessed by examining placental weight, placental morphology and genic expression in placental tissue. These measures provide an adequate representation of fetal-maternal exchange and placenta perfusion, yet true placental function is only measurable by assessing volume and oxygen content of the umbilical venous blood volume. In previous studies by Sun et al. (2015) and Ho et al. (2020), impaired umbilical venous volume and impaired fetal cardiac output were demonstrated in CHD cases. [72,75] The morphological placental abnormalities described in this review, combined with the found decreased placental blood flow in CHD cases by Sun et al. (2015) and Ho et al. (2020), suggest abnormal placental function in CHD cases.

As previously delineated, we hypothesize that fetal CHD, placental development, angiogenic alterations and neurodevelopment are all closely related. The directed acyclic

graph for these hypothetical associations is shown in Figure 2. The causal pathway of CHD and neurodevelopmental outcomes is complex and consists of numerous causal and biasing paths. In order to further clarify the causative pathway, more research is needed. In future research, we suggest a focus on the contribution of impaired placentation on neurodevelopmental delay in found CHD cases.

Another important consequence of abnormal placentation in fetal life is the susceptibility to cardiovascular disease and insulin resistance in later childhood and adult life. Abnormal placentation is related to poor fetal growth and low birthweight. Following Barker's hypothesis, these circumstances in fetal life are linked to diabetes, obesity, hypertension and coronary artery disease in adulthood. [76,77] As CHD is related to abnormal placentation, these fetuses might be more prone to developing these conditions in later life, next to their congenital heart defect. In order to identify patients at risk for cardiovascular disease and prioritize preventive measures in these cases, is important to investigate cardiovascular outcomes of CHD cases in later life.

A limitation of this review is the heterogeneity in the patient characteristics of the included studies. Most studies included all CHD cases, whereas other studies only included 'severe' or 'critical' cases. Most studies excluded cases with known genetic abnormalities, but not all studies described the methodology in this detail. Heterogeneity in the study populations may have caused differences in outcomes and error in the results. By excluding studies on fetuses with known syndromes or genetic abnormalities, a significant group of CHD cases is left out and the effect might be major in these cases. As this review seeks for the pure effect of the consequences of a CHD on placental development, patients with known genetic abnormalities were excluded, in order to efface the additional effect of the genetic abnormality. Most included studies, however, did not provide information on Whole Exome Sequencing, a technique that is developing fast and identifies single-gene abnormalities in CHD cases. [78,79] It is therefore possible that a part of the cases included in these studies which were considered as isolated CHD, may actually have a single gene disorder. Secondly, some of the studies had relatively small study populations, impeding the results to reach significant differences.

CONCLUSION

This systematic review shows that CHD is associated with lower placental weight, macroscopic and microscopic placental abnormalities, altered angiogenic biomarkers and altered genetic expression in placental tissue and maternal serum. These findings suggest impaired vascular development of both the placenta and fetal organs.

As impaired neurodevelopment is an important part of morbidity in CHD cases, future research should focus on the contribution of abnormal placentation to

neurodevelopmental outcomes of these cases. Hemodynamic consequences of the different types of CHDs should be related to placental morphology and function as well as to neurodevelopmental outcomes in utero, neonatal life, childhood and adult life. This knowledge could contribute to the development of preventive measures for CHD cases both in utero and in the entire lifespan.

REFERENCES

1. J.I. Hoffman, S. Kaplan. The incidence of congenital heart disease. J Am Coll Cardiol. 2002;39(12):1890-900. DOI: 10.1016/s0735-1097(02)01886-7.
2. T.M. Bird, C.A. Hobbs, M.A. Cleves, et al. National rates of birth defects among hospitalized newborns. Birth Defects Res A Clin Mol Teratol. 2006;76(11):762-9. DOI: 10.1002/bdra.20323.
3. P.W. Tennant, M.S. Pearce, M. Bythell, J. Rankin. 20-year survival of children born with congenital anomalies: a population-based study. Lancet. 2010;375(9715):649-56. DOI: 10.1016/S0140-6736(09)61922-X.
4. B.S. Marino, P.H. Lipkin, J.W. Newburger, et al. Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association. Circulation. 2012;126(9):1143-72. DOI: 10.1161/CIR.0b013e318265ee8a
5. F.A.R. Jansen, S.M.P. Everwijn, R. Scheepjens, et al. Fetal brain imaging in isolated congenital heart defects - a systematic review and meta-analysis. Prenat Diagn. 2016;36(7):601-13. DOI: 10.1002/pd.4842.
6. A. Khalil, S. Bennet, B. Thilaganathan, et al. Prevalence of prenatal brain abnormalities in fetuses with congenital heart disease: a systematic review. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2016;48(3):296-307. DOI: 10.1002/uog.15932
7. F.A.R. Jansen, E.W. van Zwet, M.E. Rijlaarsdam, et al. Head growth in fetuses with isolated congenital heart defects: lack of influence of aortic arch flow and ascending aorta oxygen saturation. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2016;48(3):357-64. DOI: 10.1002/uog.15980
8. A.E.L. van Nisselrooij, F.A.R. Jansen, N. van Geloven, et al. Impact of extracardiac pathology on head growth in fetuses with congenital heart defect. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2020;55(2):217-25. DOI: 10.1002/uog.20260.
9. S.M.P. Everwijn, A.I.L. Namburete, N. van Geloven, et al. Cortical development in fetuses with congenital heart defects using an automated brain-age prediction algorithm. Acta obstetricia et gynecologica Scandinavica. 2019;98(12):1595-602. DOI: 10.1111/aogs.13687.
10. S.B. Gumusoglu, A.S.S. Chilukuri, D.A. Santillan, et al. Neurodevelopmental Outcomes of Prenatal Preeclampsia Exposure. Trends Neurosci. 2020;43(4):253-68. DOI: 10.1016/j.tins.2020.02.003.
11. B.Z. Sun, D. Moster, Q.E. Harmon, A.J. Wilcox. Association of Preeclampsia in Term Births With Neurodevelopmental Disorders in Offspring. JAMA Psychiatry. 2020;77(8):823-9. DOI: 10.1001/jamapsychiatry.2020.0306.
12. T. Arcangeli, B. Thilaganathan, R. Hooper, et al. Neurodevelopmental delay in small babies at term: a systematic review. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2012;40(3):267-75. DOI: 10.1002/uog.11112.
13. Y. Nomura, R.M. John, A.B. Janssen, et al. Neurodevelopmental consequences in offspring of mothers with preeclampsia during pregnancy: underlying biological mechanism via imprinting genes. Arch Gynecol Obstet. 2017;295(6):1319-29. DOI: 10.1007/s00404-017-4347-3.
14. M.E. Kronenberg, S. Raz, C.J. Sander. Neurodevelopmental outcome in children born to mothers with hypertension in pregnancy: the significance of suboptimal intrauterine growth. Dev Med Child Neurol. 2006;48(3):200-6. DOI: 10.1017/S0012162206000430.
15. N. Auger, W.D. Fraser, J. Healy-Profitos, L. Arbour. Association Between Preeclampsia and Congenital Heart Defects. JAMA. 2015;314(15):1588-98. DOI: 10.1001/jama.2015.12505.
16. A. Ruiz, Q. Ferrer, O. Sanchez, et al. Placenta-related complications in women carrying a foetus with congenital heart disease. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2016;29(20):3271-5. DOI: 10.3109/14767058.2015.1121480.
17. G.L. Rosenthal. Patterns of prenatal growth among infants with cardiovascular malformations: possible fetal hemodynamic effects. Am J Epidemiol. 1996;143(5):505-13. DOI: 10.1093/oxfordjournals.aje.a008771.
18. I. Fantasia, W. Andrade, A. Syngelaki, et al. Impaired placental perfusion and major fetal cardiac defects. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2019;53(1):68-72. DOI: 10.1002/uog.20149.

19. J. Binder, S. Carta, J.S. Carvalho, et al. Evidence for uteroplacental malperfusion in fetuses with major congenital heart defects. PloS one. 2020;15(2):e0226741. DOI: 10.1371/journal.pone.0226741.

20. M. Donofrio. The heart–brain interaction in the fetus: Cerebrovascular blood flow in the developing human. Progress in Pediatric Cardiology. 2006;22(1):41-51. DOI: 10.1016/j.ppedcard.2006.01.004.

21. M.J. Mebius, S.A.B. Clur, A.S. Vink, et al. Growth patterns and cerebroplacental hemodynamics in fetuses with congenital heart disease. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2019;53(6):769-78. DOI: 10.1002/uog.19102.

22. A. Ruiz, M. Cruz-Lemini, N. Masoller, et al. Longitudinal changes in fetal biometry and cerebroplacental hemodynamics in fetuses with congenital heart disease. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2017;49(3):379-86. DOI: 10.1002/uog.15970.

23. M.T. Donofrio, Y.A. Bremer, R.M. Schieken, et al. Autoregulation of cerebral blood flow in fetuses with congenital heart disease: the brain sparing effect. Pediatr Cardiol. 2003;24(5):436-43. DOI:10.1007/s00246-002-0404-0.

24. J.B. Abeysekera, D.L. Gyenes, J. Atallah, et al. Fetal Umbilical Arterial Pulsatility Correlates With 2-Year Growth and Neurodevelopmental Outcomes in Congenital Heart Disease. Can J Cardiol. 2020. DOI: 10.1016/j.cjca.2020.06.024.

25. M. Arduini, P. Rosati, L. Caforio, et al. Cerebral blood flow autoregulation and congenital heart disease: possible causes of abnormal prenatal neurologic development. The journal of maternal-fetal & neonatal medicine. 2011;24(10):1208-11. DOI: 10.3109/14767058.2010.547961.

26. Y. Yamamoto, N.S. Khoo, P.A. Brooks, et al. Severe left heart obstruction with retrograde arch flow influences fetal cerebral and placental blood flow. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2013;42(3):294-9. DOI: 10.1002/uog.12448.

27. Z. Zun, G. Zaharchuk, N.N. Andescavage, et al. Non-Invasive Placental Perfusion Imaging in Pregnancies Complicated by Fetal Heart Disease Using Velocity-Selective Arterial Spin Labeled MRI. Sci Rep. 2017;7(1):16126. DOI: 10.1038/s41598-017-16461-8.

28. A.E.L. van Nisselrooij, M.A. Lugthart, S.A. Clur, et al. The prevalence of genetic diagnoses in fetuses with severe congenital heart defects. Genet Med. 2020;22(7):1206-14. DOI: 10.1038/s41436-020-0791-8.

29. J.W. Dudenhausen, R.F. Maier. Perinatal problems in multiple births. Dtsch Arztebl Int. 2010;107(38):663-8. DOI: 10.3238/arztebl.2010.0663.

30. G.A.Wells. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2013. http://www ohri ca/programs/clinical_epidemiology/oxford htm 2009 Feb 1.

31. D. Arcelli, A. Farina, C. Cappuzzello, et al. Identification of circulating placental mRNA in maternal blood of pregnancies affected with fetal congenital heart diseases at the second trimester of pregnancy: implications for early molecular screening. Prenat Diagn. 2010;30(3):229-34. DOI: 10.1002/pd.2443.

32. E. Llurba, A. Syngelaki, O. Sánchez, et al. Maternal serum placental growth factor at 11-13 weeks' gestation and fetal cardiac defects. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2013;42(2):169-74. DOI: 10.1002/uog.12346.

33. N. Andescavage, A. Yarish, M. Donofrio, et al. 3-D volumetric MRI evaluation of the placenta in fetuses with complex congenital heart disease. Placenta. 2015;36(9):1024-30. DOI: 10.1016/j.placenta.2015.06.013.

34. E. Llurba, O. Sánchez, Q. Ferrer, et al. Maternal and foetal angiogenic imbalance in congenital heart defects. Eur Heart J. 2014;35(11):701-7. DOI: 10.1093/eurheartj/eht389.

35. A. Curti, C. Lapucci, S. Berto, et al. Maternal plasma mRNA species in fetal heart defects: a potential for molecular screening. Prenat Diagn. 2016;36(8):738-43. DOI: 10.1002/pd.4853.

36. H.N. Jones, S.K. Olbrych, K.L. Smith, et al. Hypoplastic left heart syndrome is associated with structural and vascular placental abnormalities and leptin dysregulation. Placenta. 2015;36(10):1078-86. DOI: 10.1016/j.placenta.2015.08.003.

37. A. Albalawi, F. Brancusi, F. Askin, et al. Placental Characteristics of Fetuses With Congenital Heart Disease. J Ultrasound Med. 2017;36(5):965-72. DOI: 10.7863/ultra.16.04023.

38. A. Curti, C. Zucchini, I. De Maggio, et al. Fetal cardiac defects and third-trimester maternal serum placental growth factor. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2015;45(6):751-2. DOI: 10.1002/uog.14748.

39. N.B. Matthiesen, T.B. Henriksen, P. Agergaard, et al. Congenital Heart Defects and Indices of Placental and Fetal Growth in a Nationwide Study of 924 422 Liveborn Infants. Circulation. 2016;134(20):1546-56. DOI: 10.1161/CIRCULATIONAHA.116.021793.

40. E. Contro, L. Stefani, S. Berto, et al. Circulating mRNA in Maternal Plasma at the Second Trimester of Pregnancy: A Possible Screening Tool for Cardiac Conotruncal and Left Ventricular Outflow Tract Abnormalities. Mol Diagn Ther. 2017;21(6):653-61. DOI: 10.1007/s40291-017-0295-7.

41. I. Fantasia, D. Kasapoglu, T. Kasapoglu, et al. Fetal major cardiac defects and placental dysfunction at 11-13 weeks' gestation. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2018;51(2):194-8. DOI: 10.1002/uog.18839.

42. D. Morano, S. Berto, C. Lapucci, et al. Levels of Circulating mRNA for the Tenascin-X (TNXB) Gene in Maternal Plasma at the Second Trimester in Pregnancies with Isolated Congenital Ventricular Septal Defects. Mol Diagn Ther. 2018;22(2):235-40. DOI: 10.1007/s40291-018-0321-4.

43. J. Rychik, D. Goff, E. McKay, et al. Characterization of the Placenta in the Newborn with Congenital Heart Disease: Distinctions Based on Type of Cardiac Malformation. Pediatr Cardiol. 2018;39(6):1165-71. DOI: 10.1007/s00246-018-1876-x.

44. R. Takemoto, A. Anami, H. Koga. Relationship between birth weight to placental weight ratio and major congenital anomalies in Japan. PloS one. 2018;13(10):e0206002. DOI: 10.1371/journal.pone.0206002.

45. H. Miremberg, L. Gindes, L. Schreiber, et al. The association between severe fetal congenital heart defects and placental vascular malperfusion lesions. Prenat Diagn. 2019;39(11):962-7. DOI: 10.1002/pd.5515.

46. U. Radhakrishna, S. Albayrak, R. Zafra, et al. Placental epigenetics for evaluation of fetal congenital heart defects: Ventricular Septal Defect (VSD). PloS one. 2019;14(3):e0200229. DOI: 10.1371/journal.pone.0200229.

47. M.W. Russell, J.S. Moldenhauer, J. Rychik, et al. Damaging Variants in Proangiogenic Genes Impair Growth in Fetuses with Cardiac Defects. J Pediatr. 2019;213:103-9. DOI: 10.1016/j.jpeds.2019.05.013.

48. S.D. Schlatterer, J. Murnick, M. Jacobs, et al. Placental Pathology and Neuroimaging Correlates in Neonates with Congenital Heart Disease. Sci Rep. 2019;9(1):4137. DOI: 10.1038/s41598-019-40894-y.

49. J. Courtney, W. Troja, K.J. Owens, et al. Abnormalities of placental development and function are associated with the different fetal growth patterns of hypoplastic left heart syndrome and transposition of the great arteries. Placenta. 2020;101:57-65. DOI: 10.1016/j.placenta.2020.09.007.

50. V. Giorgione, V. Fesslova, S. Boveri, et al. Adverse perinatal outcome and placental abnormalities in pregnancies with major fetal congenital heart defects: a retrospective case-control study. Prenat Diagn. 2020. DOI: 10.1002/pd.5770.

51. T. Ozcan, S. Kikano, S. Plummer, et al. The Association of Fetal Congenital Cardiac Defects and Placental Vascular Malperfusion. Pediatr Dev Pathol. 2021:1093526620986497. DOI: 10.1177/1093526620986497.

52. S. Brouillet, A. Dufour, F. Prot, et al. Influence of the umbilical cord insertion site on the optimal individual birth weight achievement. Biomed Res Int. 2014;2014:341251. DOI:10.1155/2014/341251.

53. I.Y. Sun, M.T. Overgaard, C. Oxvig, L.C. Giudice. Pregnancy-associated plasma protein A proteolytic activity is associated with the human placental trophoblast cell membrane. J Clin Endocrinol Metab. 2002;87(11):5235-40. DOI: 10.1210/jc.2002-020561.

54. J. Arroyo, R.J. Torry, D.S. Torry. Deferential regulation of placenta growth factor (PlGF)-mediated signal transduction in human primary term trophoblast and endothelial cells. Placenta. 2004;25(5):379-86. DOI: 10.1016/j.placenta.2003.11.001.

55. S.Y.K.M. Park, Y.J. Kim, Y.K. Chun, et al. Placental Pathology in Intrauterine Growth Retardation. The Korean Journal of Pathology. 2002;36:30-7.

56. I. Gunyeli, E. Erdemoglu, S. Ceylaner, et al. Histopathological analysis of the placental lesions in pregnancies complicated with IUGR and stillbirths in comparison with noncomplicated pregnancies. J Turk Ger Gynecol Assoc. 2011;12(2):75-9. DOI: 10.5152/jtgga.2011.19.

57. R.S.M. Khajuria. Histopathology of placenta in intrauterine growth restriction (IUGR). International journal of research in medicine. 2019;7(3):889-92. DOI:10.18203/2320-6012.ijrms20190943.

58. M.L. Falco, J. Sivanathan, A. Laoreti, et al. Placental histopathology associated with pre-eclampsia: systematic review and meta-analysis. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2017;50(3):295-301. DOI: 10.1002/uog.17494.

59. A.O. Odibo, K.R. Patel, A. Spitalnik, et al. Placental pathology, first-trimester biomarkers and adverse pregnancy outcomes. J Perinatol. 2014;34(3):186-91. DOI: 10.1038/jp.2013.176.

60. S. Rana, S. Salahuddin, A. Mueller, et al. Angiogenic biomarkers in triage and risk for reeclampsia with severe features. Pregnancy Hypertens. 2018;13:100-6. DOI: 10.1016/j.preghy.2018.05.008.

61. P. Nikuei, K. Malekzadeh, M. Rajaei, et al. The imbalance in expression of angiogenic and anti-angiogenic factors as candidate predictive biomarker in preeclampsia. Iran J Reprod Med. 2015;13(5):251-62.

62. L.B. Andersen, R. Dechend, J.S. Jorgensen, et al. Prediction of preeclampsia with angiogenic biomarkers. Results from the prospective Odense Child Cohort. Hypertens Pregnancy. 2016;35(3):405-19. DOI: 10.3109/10641955.2016.1167219.

63. T. Chaiworapongsa, R. Romero, A.E. Whitten, et al. The use of angiogenic biomarkers in maternal blood to identify which SGA fetuses will require a preterm delivery and mothers who will develop pre-eclampsia. The journal of maternal-fetal & neonatal medicine. 2016;29(8):1214-28. DOI: 10.3109/14767058.2015.1048431.

64. I. Herraiz, E. Simon, P.I. Gomez-Arriaga, et al. Angiogenesis-Related Biomarkers (sFlt-1/PLGF) in the Prediction and Diagnosis of Placental Dysfunction: An Approach for Clinical Integration. Int J Mol Sci. 2015;16(8):19009-26. DOI: 10.3390/ijms160819009.

65. A. Conde-Agudelo, A.T. Papageorghiou, S.H. Kennedy, J. Villar. Novel biomarkers for predicting intrauterine growth restriction: a systematic review and meta-analysis. BJOG. 2013;120(6):681-94. DOI: 10.1111/1471-0528.12172.

66. J.H. Veerbeek, L. Brouwers, M.P. Koster, et al. Spiral artery remodeling and maternal cardiovascular risk: the spiral artery remodeling (SPAR) study. J Hypertens. 2016;34(8):1570-7. DOI: 10.1097/HJH.0000000000000964.

67. B.D. Gelb, W.K. Chung. Complex genetics and the etiology of human congenital heart disease. Cold Spring Harb Perspect Med. 2014;4(7):a013953. DOI: 10.1101/cshperspect.a013953.

68. Y. Dor, T.D. Camenisch, A. Itin, et al. A novel role for VEGF in endocardial cushion formation and its potential contribution to congenital heart defects. Development. 2001;128(9):1531-8. DOI: 10.1242/dev.128.9.1531.

69. C.L. Maslen. Recent Advances in Placenta-Heart Interactions. Front Physiol. 2018;9:735. DOI: 10.3389/fphys.2018.00735.

70. M.C. van Patot, G. Ebensperger, M. Gassmann, A.J. Llanos. The hypoxic placenta. High Alt Med Biol. 2012;13(3):176-84. DOI: 10.1089/ham.2012.1046.

71. A. Salihagic-Kadic, M. Medic, D. Jugovic, et al. Fetal cerebrovascular response to chronic hypoxia--implications for the prevention of brain damage. J Matern Fetal Neonatal Med. 2006;19(7):387-96. DOI: 10.1080/14767050600637861.

72. Sun L, Macgowan CK, Sled JG, et al. Reduced fetal cerebral oxygen consumption is associated with smaller brain size in fetuses with congenital heart disease. Circulation. 2015;131(15):1313-23.

73. O. Sánchez, A. Ruiz-Romero, C. Domínguez, et al. Brain angiogenic gene expression in fetuses with congenital heart disease. Ultrasound Obstet Gynecol. 2018;52(6):734-8. DOI: 10.1002/uog.18977.

74. Lawrence KM, McGovern PE, Mejaddam A, et al. Prenatal hypoxemia alters microglial morphology in fetal sheep. J Thorac Cardiovasc Surg. 2020;159(1):270-7.

75. Ho DY, Josowitz R, Katcoff H, et al. Mid-gestational fetal placental blood flow is diminished in the fetus with congenital heart disease. Prenat Diagn. 2020 Oct;40(11):1432-8.

76. Calkins K, Devaskar SU. Fetal Origins of Adult Disease. Curr Probl Pediatr Adolesc Health Care. 2011;41(6): 158–76.

77. Zanetti D, Tikkanen E, Gustafsson S, et al. Birthweight, Type 2 Diabetes and Cardiovascular Disease: Addressing the Barker Hypothesis with Mendelian randomization. Circ Gen Precis Med. 2018;11(6):e002054.

78. Bayrak CS, Zhang P, Tristani-Firouzi M, et al. De novo variants in exomes of congenital heart disease patients identify risk genes and pathways. Genome Medicine. 2020;21(9):1-18.

79. Homsy J, Zaidi S, Shen Y, et al. De novo mutations in Congenital Heart Disease with Neurodevelopmental and Other Birth Defects. Science. 2015;350(6265):1262-6.

SUPPLEMENTARY MATERIALS

Supplement 1: Quality of included studies based on the Newcastle-Ottawa assessment scale[20]

	Selection		Compara-bility	Outcome		
	Represen-tativeness of exposed cohort	*Selection of non-exposed cohort*	*Comparabil-ity of cohorts**	*Assessment of outcome*	*Adequacy of follow-up*	Total score (0-6)
Arcelli (2010)	*	*	**	*	*	******
Llurba (2013)	*	*	**	*	*	******
Andescavage (2014)	*	*	**	*		*****
Llurba (2014)	*	*	**	*	*	******
Curti (2015)		*	*	*	*	****
Jones (2015)		*	**	*	*	*****
Albalawi (2016)	*	*	**	*	*	******
Curti (2016)	*	*	**	*	*	******
Matthiesen (2016)	*	*	**	*	*	******
Contro (2017)	*	*	**	*	*	******
Fantasia (2018)	*	*	**	*	*	******
Morano (2018)	*	*	**	*	*	******
Rychik (2018)	*			*	*	***
Takemoto (2018)	*	*	**	*	*	******
Miremberg (2019)				*		*
Radhakrishna (2019)	*	*	**	*	*	******
Russell (2019)	*			*	*	***
Schlatterer (2019)	*			*	*	***
Courtney (2020)	*	*	**		*	*****
Giorgione (2020)	*	*	**	*	*	******
Ozcan (2021)	*	*	*	*	*	*****

** 2 points can be awarded*

Supplement B: Complete search string

Pubmed

((”Heart Defects, Congenital”[Mesh] OR ”congenital heart defect*”[tw] OR ”congenital heart disease*”[tw] OR ”Heart Abnormalit*”[tw] OR ”22q11 Deletion Syndrome”[tw] OR ”Alagille Syndrome”[tw] OR ”Anomalous Left Coronary Artery”[tw] OR ”Aortic Coarctation”[tw] OR ”Aortopulmonary Septal Defect”[tw] OR ”Aortopulmonary Septal Defects”[tw] OR ”Arrhythmogenic Right Ventricular Dysplasia”[tw] OR ”Barth Syndrome”[tw] OR ”Bland White Garland Syndrome”[tw] OR ”Congenitally Corrected Transposition of the Great Arteries”[tw] OR ”Cor Triatriatum”[tw] OR ”Coronary Vessel Anomalies”[tw] OR ”Coronary Vessel Anomaly”[tw] OR ”Crisscross Heart”[tw] OR ”Dextrocardia”[tw] OR ”DiGeorge Syndrome”[tw] OR ”Double Outlet Right Ventricle”[tw] OR ”Ebstein Anomaly”[tw] OR ”Ectopia Cordis”[tw] OR ”Eisenmenger Complex”[tw] OR ”Endocardial Cushion Defect”[tw] OR ”Endocardial Cushion Defects”[tw] OR ”Heart Septal Defect”[tw] OR ”Heart Septal Defects”[tw] OR ”Heterotaxy Syndrome”[tw] OR ”Hypoplastic Left Heart Syndrome”[tw] OR ”Isolated Noncompaction of the Ventricular Myocardium”[tw] OR ”Kartagener Syndrome”[tw] OR ”LEOPARD Syndrome”[tw] OR ”Levocardia”[tw] OR ”Lutembacher Syndrome”[tw] OR ”Marfan Syndrome”[tw] OR ”Myocardial Bridging”[tw] OR ”Noonan Syndrome”[tw] OR ”Patent Ductus Arteriosus”[tw] OR ”Patent Foramen Ovale”[tw] OR ”Persistent Truncus Arteriosus”[tw] OR ”Tetralogy of Fallot”[tw] OR ”Transposition of Great Vessels”[tw] OR ”Tricuspid Atresia”[tw] OR ”Trilogy of Fallot”[tw] OR ”Trisomy 13 Syndrome”[tw] OR ”Trisomy 18 Syndrome”[tw] OR ”Turner Syndrome”[tw] OR ”Univentricular Heart”[tw] OR ”congenital heart*”[tw] OR ”congenital cardiac”[tw] OR ”congenital coronary”[tw]) AND (”Placenta”[Mesh] OR ”Placenta Diseases”[Mesh] OR ”Placenta Previa”[Mesh] OR ”Placenta, Retained”[Mesh] OR ”Placenta Accreta”[Mesh] OR ”Placenta*”[tw] OR ”Placenta Diseases”[tw] OR ”Placenta Disease”[tw] OR ”Placenta Previa”[tw] OR ”Retained Placenta”[tw] OR ”Placenta Accreta”[tw] OR ”Abruptio Placentae”[tw] OR ”Chorioamnionitis”[tw] OR ”Placental Insufficiency”[tw] OR ”Placentome”[tw] OR ”Placentomes”[tw] OR ”Chorionic Villi”[tw] OR ”Decidua”[tw] OR ”Deciduoma”[tw] OR ”Trophoblasts”[tw] OR ”Trophoblast”[tw] OR ”extraplacenta*”[tw] OR ”intraplacenta*”[tw]) AND (”Fetus”[Mesh] OR ”Fetus”[tw] OR ”Foetus”[tw] OR ”fetal*”[tw] OR ”foetal*”[tw] OR ”neurodevelopment”[tw] OR ”neurodevelopment*”[tw] OR ”neuro development”[tw] OR ”neuro development*”[tw] OR ”angiogenic”[tw] OR ”angiogenic*”[tw] OR ”Angiogenic Proteins”[Mesh] OR ”Biomarkers”[Mesh] OR ”Biomarkers”[tw] OR ”biomarker”[tw] OR ”Biological Markers”[tw] OR ”Biologic Markers”[tw] OR ”Biological Markers”[tw] OR ”Biologic Marker”[tw] OR ”outcome”[tw] OR ”long outcome”[tw] OR ”outcomes”[tw] OR ”long outcomes”[tw]) NOT (”Animals”[mesh] NOT ”Humans”[mesh]) NOT ((“Case Reports”[ptyp] OR “case report”[ti]) NOT (“Review”[ptyp] OR “review”[ti] OR “Clinical Study”[ptyp] OR “trial”[ti] OR “RCT”[ti])) AND (english[la] OR dutch[la])) NOT ((”Heart Defects, Congenital”[Mesh] OR ”congenital heart defect*”[tw] OR ”congenital heart disease*”[tw] OR ”Heart Abnormalit*”[tw] OR ”22q11 Deletion Syndrome”[tw] OR ”Alagille Syndrome”[tw] OR ”Anomalous Left Coronary Artery”[tw] OR ”Aortic Coarctation”[tw] OR ”Aortopulmonary Septal Defect”[tw] OR ”Aortopulmonary Septal Defects”[tw] OR ”Arrhythmogenic Right Ventricular Dysplasia”[tw] OR ”Barth Syndrome”[tw] OR ”Bland White Garland Syndrome”[tw] OR ”Congenitally Corrected Transposition of the Great Arteries”[tw] OR ”Cor Triatriatum”[tw] OR ”Coronary Vessel Anomalies”[tw] OR ”Coronary Vessel Anomaly”[tw] OR ”Crisscross Heart”[tw] OR ”Dextrocardia”[tw] OR ”DiGeorge Syndrome”[tw] OR ”Double Outlet Right Ventricle”[tw] OR ”Ebstein Anomaly”[tw] OR ”Ectopia Cordis”[tw] OR ”Eisenmenger Complex”[tw] OR ”Endocardial Cushion Defect”[tw] OR ”Endocardial Cushion Defects”[tw] OR ”Heart Septal Defect”[tw] OR ”Heart Septal Defects”[tw] OR ”Heterotaxy Syndrome”[tw] OR ”Hypoplastic Left Heart Syndrome”[tw] OR ”Isolated 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”Placental Insufficiency”[tw] OR ”Placentome”[tw] OR ”Placentomes”[tw]

OR "Chorionic Villi" [tw] OR "Decidua" [tw] OR "Deciduoma" [tw] OR "Trophoblasts" [tw] OR "Trophoblast" [tw] OR "extraplacenta*" [tw] OR "intraplacenta*" [tw]) AND ("Fetus" [Mesh] OR "Fetus" [tw] OR "Foetus" [tw] OR "fetal*" [tw] OR "foetal*" [tw]) NOT ("Animals" [mesh] NOT "Humans" [mesh]) NOT (("Case Reports" [ptyp] OR "case report" [ti]) NOT ("Review" [ptyp] OR "review" [ti] OR "Clinical Study" [ptyp] OR "trial" [ti] OR "RCT" [ti])) AND (english [la] OR dutch [la]))

Embase

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Web of Science

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Cochrane

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Emcare

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ti,ab OR “congenital coronary”.ti,ab) AND (exp *”Placenta”/ OR exp *”Placenta Disorder”/ OR “Placenta*”.ti,ab OR “Placenta Diseases”.ti,ab OR “Placenta Disease”.ti,ab OR “Placenta Previa”.ti,ab OR “Retained Placenta”.ti,ab OR “Placenta Accreta”.ti,ab OR “Abruptio Placentae”. ti,ab OR “Chorioamnionitis”.ti,ab OR “Placental Insufficiency”.ti,ab OR “Placentome”.ti,ab OR “Placentomes”.ti,ab OR “Chorionic Villi”.ti,ab OR “Decidua”.ti,ab OR “Deciduoma”.ti,ab OR “Trophoblasts”.ti,ab OR “Trophoblast”.ti,ab OR “extraplacenta*”.ti,ab OR “intraplacenta*”.ti,ab) AND (*”Fetus”/ OR “Fetus”.ti,ab OR “Foetus”.ti,ab OR “fetal*”.ti,ab OR “foetal*”.ti,ab) NOT (exp “Animals”/ NOT exp “Humans”/) NOT ((“Case Report”/ OR “case report”.ti) NOT (“Review”/ OR “review”.ti OR “Clinical Study”/ OR “trial”.ti OR “RCT”.ti OR exp “clinical trial”/)) AND (english.la OR dutch.la)).

GENETICS

Pubmed

((“Heart Defects, Congenital” majr OR “congenital heart defect*” ti OR “congenital heart disease*” ti OR “Heart Abnormalit*” ti OR “22q11 Deletion Syndrome” ti OR “Alagille Syndrome” ti OR “Anomalous Left Coronary Artery” ti OR “Aortic Coarctation” ti OR “Aortopulmonary Septal Defect” ti OR “Aortopulmonary Septal Defects” ti OR “Arrhythmogenic Right Ventricular Dysplasia” ti OR “Barth Syndrome” ti OR “Bland White Garland Syndrome” ti OR “Congenitally Corrected Transposition of the Great Arteries” ti OR “Cor Triatriatum” ti OR “Coronary Vessel Anomalies” ti OR “Coronary Vessel Anomaly” ti OR “Crisscross Heart” ti OR “Dextrocardia” ti OR “DiGeorge Syndrome” ti OR “Double Outlet Right Ventricle” ti OR “Ebstein Anomaly” ti OR “Ectopia Cordis” ti OR “Eisenmenger Complex” ti OR “Endocardial Cushion Defect” ti OR “Endocardial Cushion Defects” ti OR “Heart Septal Defect” ti OR “Heart Septal Defects” ti OR “Heterotaxy Syndrome” ti OR “Hypoplastic Left Heart Syndrome” ti OR “Isolated Noncompaction of the Ventricular Myocardium” ti OR “Kartagener Syndrome” ti OR “LEOPARD Syndrome” ti OR “Levocardia” ti OR “Lutembacher Syndrome” ti OR “Marfan Syndrome” ti OR “Myocardial Bridging” ti OR “Noonan Syndrome” ti OR “Patent Ductus Arteriosus” ti OR “Patent Foramen Ovale” ti OR “Persistent Truncus Arteriosus” ti OR “Tetralogy of Fallot” ti OR “Transposition of Great Vessels” ti OR “Tricuspid Atresia” ti OR “Trilogy of Fallot” ti OR “Trisomy 13 Syndrome” ti OR “Trisomy 18 Syndrome” ti OR “Turner Syndrome” ti OR “Univentricular Heart” ti OR “congenital heart*” ti OR “congenital cardiac” ti OR “congenital coronary” ti) AND (“Fetus” Mesh OR “Fetus” tw OR “Foetus” tw OR “fetal*” tw OR “foetal*” tw) AND (“Heart Defects, Congenital/genetics” majr OR “genetics” ti OR “genetic*” ti OR “Genetic Techniques” majr OR “Genetic Phenomena” majr OR “RNA” majr OR “RNA” ti OR “DNA” majr OR “DNA” ti OR “Sequence Analysis” majr OR “Sequence Analysis” ti OR “sequencing” ti) NOT (“Animals” mesh NOT “Humans” mesh) NOT ((“Case Reports” ptyp OR “case report” ti) NOT (“Review” ptyp OR “review” ti OR “Clinical Study” ptyp OR “trial” ti OR “RCT” ti)) AND (english la OR dutch la))

Embase

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Cochrane

((”congenital heart disease” OR ”congenital heart defect*” OR ”congenital heart disease*” OR ”Heart Abnormalit*” OR ”22q11 Deletion Syndrome” OR ”Alagille Syndrome” OR ”Anomalous Left Coronary Artery” OR ”Aortic Coarctation” OR ”Aortopulmonary Septal Defect” OR ”Aortopulmonary Septal Defects” OR ”Arrhythmogenic Right Ventricular Dysplasia” OR ”Barth Syndrome” OR ”Bland White Garland Syndrome” OR ”Congenitally Corrected Transposition of the Great Arteries” OR

”Cor Triatriatum” OR ”Coronary Vessel Anomalies” OR ”Coronary Vessel Anomaly” OR ”Crisscross Heart” OR ”Dextrocardia” OR ”DiGeorge Syndrome” OR ”Double Outlet Right Ventricle” OR ”Ebstein Anomaly” OR ”Ectopia Cordis” OR ”Eisenmenger Complex” OR ”Endocardial Cushion Defect” OR ”Endocardial Cushion Defects” OR ”Heart Septal Defect” OR ”Heart Septal Defects” OR ”Heterotaxy Syndrome” OR ”Hypoplastic Left Heart Syndrome” OR ”Isolated Noncompaction of the Ventricular Myocardium” OR ”Kartagener Syndrome” OR ”LEOPARD Syndrome” OR ”Levocardia” OR ”Lutembacher Syndrome” OR ”Marfan Syndrome” OR ”Myocardial Bridging” OR ”Noonan Syndrome” OR ”Patent Ductus Arteriosus” OR ”Patent Foramen Ovale” OR ”Persistent Truncus Arteriosus” OR ”Tetralogy of Fallot” OR ”Transposition of Great Vessels” OR ”Tricuspid Atresia” OR ”Trilogy of Fallot” OR ”Trisomy 13 Syndrome” OR ”Trisomy 18 Syndrome” OR ”Turner Syndrome” OR ”Univentricular Heart” OR ”congenital heart*” OR ”congenital cardiac” OR ”congenital coronary”) AND (”Placenta” OR ”Placenta Disorder” OR ”Placenta*” OR ”Placenta Diseases” OR ”Placenta Disease” OR ”Placenta Previa” OR ”Retained Placenta” OR ”Placenta Accreta” OR ”Abruptio Placentae” OR ”Chorioamnionitis” OR ”Placental Insufficiency” OR ”Placentome” OR ”Placentomes” OR ”Chorionic Villi” OR ”Decidua” OR ”Deciduoma” OR ”Trophoblasts” OR ”Trophoblast” OR ”extraplacenta*” OR ”intraplacenta*”) AND (”Fetus” OR ”Fetus” OR ”Foetus” OR ”fetal*” OR ”foetal*”) AND (”genetics” OR ”genetic*” OR ”genetics” OR ”Genetic Procedures” OR ”heredity” OR ”RNA” OR ”RNA” OR ”DNA” OR ”DNA” OR ”Sequence Analysis” OR ”Sequence Analysis” OR ”sequencing”)):ti,ab,kw NOT (conference abstract):pt

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((exp *”congenital heart disease”/ OR ”congenital heart defect*”.ti,ab OR ”congenital heart disease*”.ti,ab OR ”Heart Abnormalit*”.ti,ab OR ”22q11 Deletion Syndrome”.ti,ab OR ”Alagille Syndrome”.ti,ab OR ”Anomalous Left Coronary Artery”.ti,ab OR ”Aortic Coarctation”.ti,ab OR ”Aortopulmonary Septal Defect”.ti,ab OR ”Aortopulmonary Septal Defects”.ti,ab OR ”Arrhythmogenic Right Ventricular Dysplasia”.ti,ab OR ”Barth Syndrome”.ti,ab OR ”Bland White Garland Syndrome”.ti,ab OR ”Congenitally Corrected Transposition of the Great Arteries”.ti,ab OR ”Cor Triatriatum”.ti,ab OR ”Coronary Vessel Anomalies”.ti,ab OR ”Coronary Vessel Anomaly”.ti,ab OR ”Crisscross Heart”.ti,ab OR ”Dextrocardia”.ti,ab OR ”DiGeorge Syndrome”.ti,ab OR ”Double Outlet Right Ventricle”.ti,ab OR ”Ebstein Anomaly”.ti,ab OR ”Ectopia Cordis”.ti,ab OR ”Eisenmenger Complex”.ti,ab OR ”Endocardial Cushion Defect”.ti,ab OR ”Endocardial Cushion Defects”.ti,ab OR ”Heart Septal Defect”.ti,ab OR ”Heart Septal Defects”.ti,ab OR ”Heterotaxy Syndrome”.ti,ab OR ”Hypoplastic Left Heart Syndrome”.ti,ab OR ”Isolated Noncompaction of the Ventricular Myocardium”.ti,ab OR ”Kartagener Syndrome”.ti,ab OR ”LEOPARD Syndrome”.ti,ab OR ”Levocardia”.ti,ab OR ”Lutembacher Syndrome”.ti,ab OR ”Marfan Syndrome”.ti,ab OR ”Myocardial Bridging”.ti,ab OR ”Noonan Syndrome”.ti,ab OR ”Patent Ductus Arteriosus”.ti,ab OR ”Patent Foramen Ovale”.ti,ab OR ”Persistent Truncus Arteriosus”.ti,ab OR ”Tetralogy of Fallot”.ti,ab OR ”Transposition of Great Vessels”.ti,ab OR ”Tricuspid Atresia”.ti,ab OR ”Trilogy of Fallot”.ti,ab OR ”Trisomy 13 Syndrome”.ti,ab OR ”Trisomy 18 Syndrome”.ti,ab OR ”Turner Syndrome”.ti,ab OR ”Univentricular Heart”.ti,ab OR ”congenital heart*”.ti,ab OR ”congenital cardiac”.ti,ab OR ”congenital coronary”.ti,ab) AND (exp ”Placenta”/ OR exp ”Placenta Disorder”/ OR ”Placenta*”.mp OR ”Placenta Diseases”.mp OR ”Placenta Disease”.mp OR ”Placenta Previa”.mp OR ”Retained Placenta”.mp OR ”Placenta Accreta”.mp OR ”Abruptio Placentae”.mp OR ”Chorioamnionitis”.mp OR ”Placental Insufficiency”.mp OR ”Placentome”.mp OR ”Placentomes”.mp OR ”Chorionic Villi”.mp OR ”Decidua”.mp OR ”Deciduoma”.mp OR ”Trophoblasts”.mp OR ”Trophoblast”.mp OR ”extraplacenta*”.mp OR ”intraplacenta*”.mp) AND (”Fetus”/ OR ”Fetus”.mp OR ”Foetus”.mp OR ”fetal*”.mp OR ”foetal*”.mp) AND (”genetics”.mp OR ”genetic*”.mp OR exp ”genetics”/ OR ”Genetic Procedures”/ OR exp ”heredity”/ OR exp ”RNA”/ OR ”RNA”.mp OR exp ”DNA”/ OR ”DNA”.mp OR exp ”Sequence Analysis”/ OR ”Sequence Analysis”.mp OR ”sequencing”.mp) NOT (exp ”Animals”/ NOT exp ”Humans”/) NOT ((“Case Report”/ OR “case report”.ti) NOT (“Review”/ OR “review”.ti OR “Clinical Study”/ OR “trial”.ti OR “RCT”.ti OR exp “clinical trial”/)) AND (english.la OR dutch.la)) NOT (conference review or conference abstract).pt