# The placenta in fetal congenital heart disease

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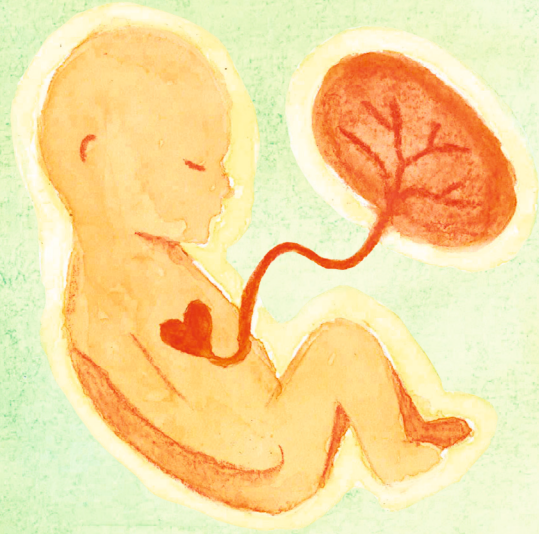

CHAPTER 8

# Pregnancy complications in fetal congenital heart disease: a result of common early developmental pathways rather than fetal hemodynamics

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# ABSTRACT

## Objective

The aim of this study was to compare placenta-related complications between different types of fetal CHD, based on cardiac hemodynamics.

## Method

All CHD cases diagnosed prenatally during 2009-2023 were selected. Exclusion criteria were: multiple pregnancies, pregnancy termination and diagnosed genetic anomalies. Cases were categorized into 6 groups based on hemodynamic factors.

## Results

After exclusion, 1293 cases were available for analysis. The incidence of fetal growth restriction (FGR) was 198/1247 (15.9%). There was a significant difference in FGR between the groups of CHD (p=0.002), though it could not be related to aortic flow and oxygenation. There was a high incidence of preeclampsia (PE) (64/1282, 5.0%), pregnancy induced hypertension (PIH) (43/1284, 3.3%) and intra uterine fetal demise (IUFD) (33/1291, 2.6%) in our cohort as compared to reference values. Nonetheless, there were no differences in PE, PIH and IUFD between the different CHD groups.

## Conclusion

A high incidence of placenta related complications was found, though this could not be related to fetal hemodynamics. Even in CHDs without hemodynamic changes, a high incidence of these complications was found. Early embryological developmental pathways affecting the placenta and the fetal heart might cause altered placental development and induce placentally related complications.

# INTRODUCTION

Congenital heart defects (CHD) represent the most prevalent congenital anomalies, with an incidence of five to eight per thousand newborns [1]. Advancements in medical care have led to significant improvements in survival rates and consequently, focus of research has shifted towards long-term outcomes and quality of life. [1-3] Children and adolescents with CHD are reported to frequently have neurodevelopmental delays and this aspect has become an integral component in prenatal counseling. [4-11] Altered neurodevelopment is already starting in utero, as evidenced by fetal imaging studies.[1-5].

The earliest hypotheses to explain impaired fetal brain growth in utero pointed towards diminished cerebral blood flow or decreased oxygenation in the ascending aorta during fetal development, induced by the anatomy of the heart defect. [1-5] In recent studies however, decreased fetal growth and placental insufficiency were found to be important determinants influencing brain growth in fetal CHD. [6-9] Therefore the impact of other intrauterine factors on fetal brain development in these cases should not be underestimated.

Fetal growth restriction (FGR), pregnancy induced hypertension (PIH) and preeclampsia (PE) have their etiological roots in placental dysfunction and are more frequently observed in pregnancies complicated by fetal CHD.[10-17] Given the association between placental insufficiency, diminished fetal growth, maternal hypertensive disorders and the potentially negative influence on brain development in CHD fetuses, combined with a higher incidence of placental disorders, a notable knowledge gap has emerged concerning this potential interplay. It has been described that shared developmental pathways influence both the placenta and the fetal heart.[18,19] This raises the question whether fetal cardiac hemodynamics in CHD influence placental development, thereby contributing to placenta related complications, like PE and FGR.

In this cohort study, the incidence of pregnancy complications is studied in fetal CHD. To assess the hemodynamic effect of the different heart defects on these outcomes, CHD cases are classified into groups based on aortic oxygenation and flow. We hypothesize that CHD cases causing alterations in fetal hemodynamics are prone to decreased fetal-maternal exchange of oxygens and nutrients through the placenta and are therefore more at risk for placenta related complications, such as PE, PIH and FGR.

# METHODS

## Patient selection

Cases with a prenatally identified CHD, born between January 2009 and 2023 were extracted from the PRECOR registry. This registry prospectively includes all fetal and neonatal cases with CHD from the Center for Congenital Heart Abnormalities Amsterdam-

Leiden (CAHAL), which is a collaboration of two academic hospitals (Amsterdam University Medical Center and Leiden University Medical Centre). Cases with primary fetal arrhythmias are not included. The methodology of the data collection for this registry has been described previously and is in accordance with the Dutch legal and ethical standards for medical research, in which individual consent is waived for large registry studies in which individuals are not identifiable.[20]

## Data collection

After identification of cases, additional data on cardiac diagnosis, maternal characteristics (age, parity, medical history, obstetric history), fetal characteristics (gender, fetal growth, extra-cardiac malformations, genetic test results) and data on the course of pregnancy (gestational age of delivery, pregnancy complications) were collected from electronic patient files. Fetal cardiac diagnoses were categorized as previously described.[20] Cases with a genetic abnormality or a syndrome, multiple pregnancies and cases in which the pregnancy was terminated, were excluded from the analysis.

Preexistent hypertension, PIH and PE were defined according to the ISSHP classification.[21] PE was defined according to the latest ISSHP definition (including cases with PIH and FGR without proteinuria and cases with FGR and proteinuria without PIH). Fetal growth restriction (FGR) was defined as birthweight below the 10$^{th}$ percentile. Maternal obesity was defined as Body Mass Index ›30.

## CHD groups

Cases were categorized into six different categories of CHD, based on theoretical aortic arch flow and oxygenation, as previously described.[22] In short: group 1 consists of cases with normal aortic flow + low oxygenation (including simple transposition of the great arteries (TGA)), group 2 of cases with obstructed aortic flow + normal oxygenation (forward flow in the aortic arch, including aortic coarctation), group 3 obstructed aortic flow, with reversed aortic arch flow + mixed oxygenation (including hypoplastic left heart syndrome (HLHS)), group 4 with obstructed aortic arch flow + mixed oxygenation (forward flow in the aortic arch, including tricuspid atresia), group 5 with normal aortic flow + mixed oxygenation (including double outlet left ventricle (DORV)), group 6 with normal aortic flow + normal oxygenation (including small ventricular septal defect (VSD)). Details of the allocation can be found in Appendix A. In addition, different CHD groups were combined based on flow and oxygenation (group 1+5 including CHD cases with normal aortic arch flow and low/mixed oxygenation, group 3+4 including CHD cases with obstructed/reversed aortic flow and mixed oxygenation).

## Statistical analysis

Continuous non-normally distributed data were presented as median ± interquartile range (IQR). Categorical data were presented as numbers and percentages (n, %).

Chi-square tests were used where appropriate. Additional multivariate analyses were performed to correct for possible confounders. A p-value of ‹0.05 was considered significant. Statistical analyses were performed using IBM SPSS Statistics 29.0 (IBM, Armonk, NY, USA).

# RESULTS

## Case selection

We extracted 2370 CHD cases from the PRECOR registry (Table 1) fulfilling the inclusion criteria. Of these, 1077 cases were excluded: 184 multiple pregnancies, 280 terminations of pregnancy and 608 with a genetic anomaly (Figure 1). In addition, 5 cases were lost to follow up due to moving abroad.

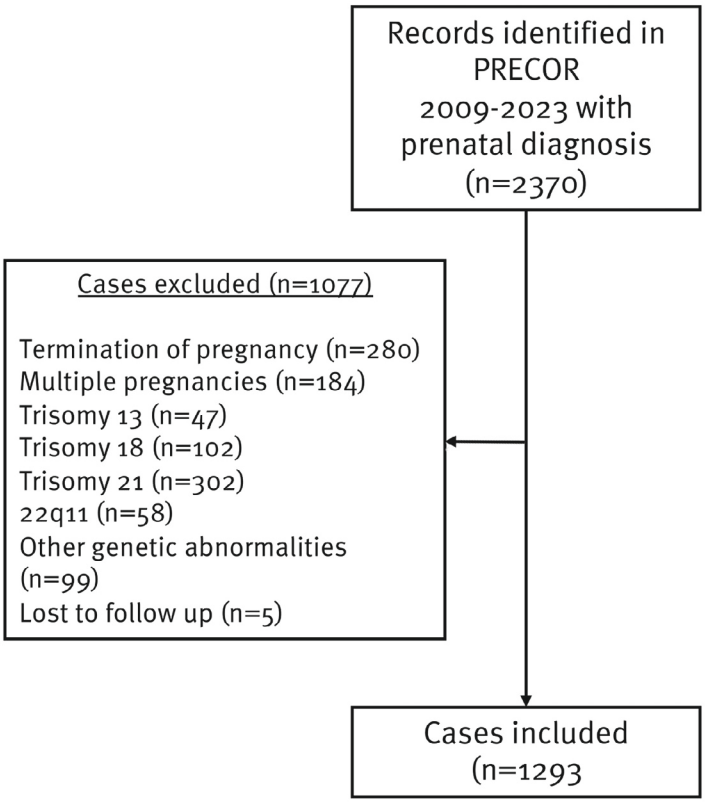


**Figure 1: Flowchart of included cases**

**Table 1. Baseline characteristics of included cases and per CHD group**

| | Total (n=1293) | Group 1† (n=142) | Group 2‡ (n=210) | Group 3§ (n=89) | Group 4¶ (n=137) | Group 5 †† (n=272) | Group 6 ‡‡ (n=443) | p-value |
|---|---|---|---|---|---|---|---|---|
| Maternal age (median, IQR) | 31 (7) | 31 (5) | 32 (7) | 31 (7) | 30 (7) | 31 (7) | 32 (8) | **0.044** |
| Maternal illness (n, %) | 201/1276 (15.8) | 17/141 (12.1) | 35/206 (17.0) | 15/88 (17.0) | 18/134 (13.4) | 55/269 (20.4) | 61/438 (13.9) | 0.161 |
| Maternal obesity (n, %) | 162/1179 (10.7) | 16/135 (11.9) | 16/186 (8.6) | 17/80 (21.3) | 26/129 (20.2) | 36/251 (14.3) | 51/398 (12.8) | **0.022** |
| Maternal smoking (n, %) | 45/1261 (3.3) | 6/142 (4.2) | 9/201 (4.5) | 3/86 (3.5) | 5/133 (3.8) | 10/264 (3.8) | 12/435 (2.8) | 0.908 |
| Maternal teratogenic medication (n, %) | 23/1284 (1.8) | 1/142 (0.7) | 7/207 (3.4) | 2/88 (2.3) | 3/135 (2.2) | 4/271 (1.5) | 6/441 (1.4) | 0.440 |
| Maternal parity (n, %) | n=1241 | n=139 | n=191 | n=86 | n=135 | n=260 | n=430 | **0.015** |
| 0 | 567 (45.7) | 57 (41.0) | 83 (43.5) | 42 (48.8) | 61 (45.2) | 123 (47.3) | 201 (46.7) | |
| 1 | 432 (34.8) | 61 (43.9) | 66 (34.6) | 29 (33.7) | 45 (33.3) | 77 (29.6) | 154 (35.8) | |
| 2 | 161 (13.0) | 15 (10.8) | 27 (14.1) | 9 (10.5) | 16 (11.9) | 43 (16.5) | 51 (11.9) | |
| 3 | 59 (4.8) | 5 (3.6) | 11 (5.8) | 5 (5.8) | 6 (0.4) | 14 (5.4) | 18 (4.2) | |
| >3 | 22 (1.8) | 1 (0.7) | 4 (2.1) | 1 (1.2) | 7 (5.2) | 3 (1.2) | 6 (1.4) | |
| Preexistent hypertension (n, %) | 9/1287 (7.0) | 1/142 (0.7) | 1/209 (0.5) | 1/88 (1.1) | 0/135 | 4/271 (1.5) | 2/442 (4.5) | 0.538 |
| Preexistent diabetes mellitus (n, %) | 20/1287 (1.6) | 0/142 | 2/208 (1.0) | 3/88 (3.4) | 1/135 (0.7) | 8/271 (3.0) | 6/443 (1.4) | 0.115 |
| Gestational age at time of delivery in weeks (n, %) | n=1276 | n=140 | n=207 | n=89 | n=136 | n=270 | n=434 | **0.002** |
| <37 | 183 (14.3) | 8 (5.7) | 41 (19.8) | 10 (11.2) | 9 (6.6) | 44 (16.3) | 71 (16.4) | |
| 37-40 | 757 (59.3) | 97 (69.3) | 121 (58.5) | 54 (60.7) | 91 (66.9) | 155 (57.4) | 239 (55.1) | |
| >40 | 336 (26.3) | 35 (25.0) | 45 (21.7) | 25 (28.1) | 36 (26.5) | 71 (26.3) | 124 (28.6) | |
| Fetal gender (n, %) | n=1283 | n=141 | n=209 | n=89 | n=134 | n=271 | n=439 | **<0.001** |
| Male | 731 (57.0) | 95 (67.4) | 140 (67.0) | 50 (56.2) | 78 (58.2) | 150 (55.4) | 218 (49.7) | |
| Female | 552 (43.0) | 46 (32.6) | 69 (33.0) | 39 (43.8) | 56 (41.8) | 121 (44.6) | 221 (50.3) | |

† *normal aortic arch flow, low oxygenation;* ‡ *obstructed aortic flow, normal oxygenation;* § *reversed aortic arch flow, mixed oxygenation;* ¶ *obstructed aortic arch flow, mixed oxygenation;* †† *normal aortic arch flow, mixed oxygenation;* ‡‡ *normal aortic arch flow, normal oxygenation*

## Study subject characteristics

Patient characteristics are shown in Table 1. There were no significant differences in maternal medical history and medication between the groups (including pre-existent hypertension and pre-existent diabetes mellitus). Maternal age was significantly different between the groups (p=0.022), however the differences was so small (largest mean difference of two years) that it is considered clinically irrelevant. Likewise in parity (p=0.015, with a largest difference of 6.3% in the nulliparae group) and gestational age at delivery (p=0.002, with a largest difference of 14.2% in the 37-40 weeks group). There was significantly more maternal obesity in the groups with reversed and obstructed aortic flow with mixed oxygenation (group 3 and 4: including HLHS and arch hypoplasia/coarctation) as compared to the other groups (21.3% in group 3, 20.2% in group 4, 10.7% in total CHD population, p=0.022). When combining CHD groups based on cardiac and aortic hemodynamics, there was no significant difference in maternal obesity between cases with normal aortic arch flow and low/mixed oxygenation (group 1+5, 52/414, 12.6%) and cases with obstructed aortic arch flow and normal oxygenation (group 2, 8.6%) (p=0.092).

There was a significant difference in fetal gender between the groups, as in cases with normal aortic flow and low oxygenation (group 1) and cases with obstructed aortic flow and normal oxygenation (group 2) there were more males, whereas in the group with normal aortic flow and normal oxygenation (group 6) male/female gender was equally distributed (p<0.001).

## Pregnancy complications per group of CHD

Of the 1293 included CHD cases, 5.0% had PE, 3.3% had PIH, 15.9% had FGR and 2.6% had IUFD (Table 2). When comparing all CHD groups, no difference was found in the incidence of PE, PIH and intra-uterine fetal demise (IUFD). FGR occurred significantly more frequently in group 5 and 6 (p=0.002), representing cases with normal aortic arch flow and mixed oxygenation (including DORV and hypoplastic right heart syndrome (HRHS) in group 5) and normal aortic arch flow and normal oxygenation (including isolated small VSD, persistent left superior vena cava (PLSVC) and right aortic arch (RAA) in group 6). Group 1 (included cases with simple TGA) and group 4 (including cases with complex TGA) had the lowest incidence of PE (4.2% in group 1, 2.9% in group 4), PIH (2.8% in group 1, 1.5% in group 4) and FGR (8.6% in group 1, 8.4% in group 4).

When combining the hemodynamic CHD groups based on their effect on aortic flow and oxygenation, more FGR was reported in cases with normal aortic arch flow, independent of the oxygenation (group 1+5, including simple TGA, DORV, HRHS and group 6, including isolated small VSD, PLSVC, RAA) (p=0.030) (Table 3). When comparing CHD cases with normal aortic flow and low/mixed oxygenation (group 1+5, including simple TGA, DORV, HRHS) with cases with obstructed aortic flow with normal oxygenation (group 2, including hypoplasia/coarctation/interruption of the aorta), no difference was found in FGR (p=0.787) (Table 4). When combining CHD groups based on flow and oxygenation as in Table 3 and Table 4, no differences were found in PE, PIH and IUFD.

**Table 2. Pregnancy outcomes per CHD group**

| | **Total** (n=1293, 100%) | **Group 1†** (n=142, 11.0%) | **Group 2‡** (n=210, 16.2%) | **Group 3‡** (n=89, 6.9%) | **Group 4¶** (n=137, 10.6%) | **Group 5 ††** (n=272, 21.0%) | **Group 6 ‡‡** (n=443, 34.3%) | **p-value** |
|---|---|---|---|---|---|---|---|---|
| PE (n, %) | 64/1282 (5.0) | 6/142 (4.2) | 13/207 (6.3) | 4/89 (4.5) | 4/136 (2.9) | 16/271 (5.9) | 21/437 (4.8) | 0.752 |
| PIH (n, %) | 43/1284 (3.3) | 4/142 (2.8) | 9/207 (4.3) | 4/89 (4.5) | 2/136 (1.5) | 12/271 (4.4) | 12/439 (2.7) | 0.536 |
| FGR (n, %) | 198/1247 (15.9) | 12/139 (8.6) | 32/205 (15.6) | 10/87 (11.5) | 11/131 (8.4) | 55/268 (20.5) | 78/417 (18.7) | **0.002** |
| IUFD (n, %) | 33/1291 (2.6) | 0/142 | 3/210 (1.4) | 4/89 (4.5) | 4/135 (3.0) | 8/272 (2.9) | 14/443 (3.2) | 0.218 |

*FGR = fetal growth restriction, IUFD = intra uterine fetal demise, PE =preeclampsia, PIH =pregnancy induced hypertension; † normal aortic arch flow, low oxygenation; ‡ obstructed aortic flow, normal oxygenation; § reversed aortic arch flow, mixed oxygenation; ¶ obstructed aortic arch flow, mixed oxygenation; †† normal aortic arch flow, mixed oxygenation; ‡‡ normal aortic arch flow, normal oxygenation*

**Table 3. Pregnancy outcomes in CHD groups combined based on flow and oxygenation**

| | **Total** (n=1293) | **Group 1+5†** (n=414, 32.0%) | **Group 2‡** (n=210, 16.2%) | **Group 3+4§** (n=226, 17.5%) | **Group 6¶** (n=443, 34.3%) | **p-value** |
|---|---|---|---|---|---|---|
| PE (n, %) | 64/1282 (5.0) | 22/413 (5.3) | 13/207 (6.3) | 8/225 (3.6) | 21/437 (4.8) | 0.608 |
| PIH (n, %) | 43/1284 (3.3) | 16/413 (3.9) | 9/207 (4.3) | 6/225 (2.7) | 12/439 (2.7) | 0.609 |
| FGR (n, %) | 198/1247 (15.9) | 78/417 (18.7) | 32/205 (15.6) | 21/218 (9.6) | 78/417 (18.7) | 0.030 |
| IUFD (n, %) | 33/1291 (2.6) | 8/414 (1.9) | 3/210 (1.4) | 8/224 (3.6) | 14/443 (3.2) | 0.348 |

*FGR = fetal growth restriction, IUFD = intra uterine fetal demise, PE =preeclampsia, PIH =pregnancy induced hypertension; † Group 1+5 = normal aortic arch flow, low/mixed oxygenation; ‡ Group 2 = obstructed aortic arch flow, normal oxygenation; § Group 3+4 = obstructed/reversed aortic arch flow, mixed oxygenation; ¶ Group 6 = normal aortic arch flow, normal oxygenation*

**Table 4. Pregnancy outcomes in CHD with low/mixed oxygenation and CHD with obstructed aorta flow**

| | **Total** (n=624) | **Group 1+5†** (n=414, 66.3%) | **Group 2‡** (n=210, 33.7%) | **p-value** |
|---|---|---|---|---|
| PE (n, %) | 29/620 (4.7) | 22/413 (5.3) | 13/207 (6.3) | 0.434 |
| PIH (n, %) | 25/620 (4.0) | 16/413 (3.9) | 9/207 (4.3) | 0.777 |
| FGR (n, %) | 99/612 (16.2) | 78/417 (18.7) | 32/205 (15.6) | 0.787 |
| IUFD (n, %) | 11/624 (1.8) | 8/414 (1.9) | 3/210 (1.4) | 0.651 |

*FGR = fetal growth restriction, IUFD = intra uterine fetal demise, PE =preeclampsia, PIH =pregnancy induced hypertension; † Group 1+5 = normal aortic arch flow, low/mixed oxygenation; ‡ Group 2 = obstructed aortic arch flow, normal oxygenation*

# DISCUSSION

In this prospective cohort study with a large set of consecutively included fetuses, we found a high incidence of PE, PIH, FGR and IUFD in CHD cases. We found no differences in PE, PIH and IUFD between the studied CHD groups. These results suggest that abnormal placenta development is present in all types of CHD, including minor malformations, but there is no or a limited effect of cardiac hemodynamics on placental development and function. As all types of fetal CHD are susceptible to placenta related complications, awareness to these complications should not be restricted to cases that show the largest hemodynamic alterations.

In accordance with previous literature [10-16], all pregnancy related complications were more common in our cohort as compared to the overall Dutch and/or European population. In The Netherlands, the incidence of PE has previously been described as 2.2%, whereas in our cohort 5.0% had PE (OR = 2.27).[23] The incidence of PIH in Europe is 2.3-3.0%, in this CHD cohort slightly higher (3.3%, OR = 1.10 – 1.43).[24] FGR was defined as birthweight <10$^{th}$ percentile, though as much as 15.9% of our cohort had FGR (OR = 1.59). The incidence of IUFD in our cohort was 2.6%, compared to only 0.44% in the Dutch population (OR = 5.91).[25]

The only parameter that differed in prevalence between the cardiac diagnoses was FGR. The CHD group with normal aortic flow and normal oxygenation (group 6) had more FGR. Nevertheless, when combining the groups based on hemodynamics and comparing only cases with *normal* aortic flow and low/mixed oxygenation (group 1+5) with cases with *obstructed* aortic flow and normal oxygenation (group 2), no significant difference in FGR could be established. The difference in FGR between the groups can therefore not be related to cardiac and aortic hemodynamics, but seems the effect of random error.

As the high incidence of placenta related complications in pregnancies with fetal CHD cannot be related to fetal hemodynamics, the results of our study support the hypothesis

that there is a limited effect of cardiac and aortic hemodynamics on placental development in fetal CHD. This corresponds with the hypothesis that placental development and embryonic heart development occur in parallel and directly affect each other in early gestation, as demonstrated in previous literature.[26-28] Altered placental development in fetal CHD can be related to the common early embryological developmental pathways of the placenta and the fetal heart, rather than solely to hemodynamic alterations in the fetal circulation caused by the CHD. The fact that we found no differences in the occurrence of placenta related complications between our CHD-groups supports this theory. In addition, it is striking that the groups including cases with simple and complex TGA had the lowest incidence of PE, PIH and FGR. This corresponds to the hypothesis that early embryological factors may play a role. Subsequently, alterations in early placental development can contribute to the described PE, PIH, FGR and IUFD in pregnancies with fetal CHD, rather than the other way around. In parallel, we hypothesize that these early developmental alterations can contribute to the neurodevelopmental delay that is described in fetal CHD as well. [29]

## Clinical implications

It is already known that PE, PIH, FGR and IUFD have a higher incidence in fetal CHD. However, clinicians tend to only be aware of these complications in CHD with large hemodynamic alterations like univentricular heart defects. Yet, we found a high frequency of placenta related complications in *all* types of CHD (as compared to the Dutch and/or European population), also in the CHDs that cause less or no hemodynamic changes in the circulation (small VSD). Therefore, it is important to adequately monitor both the maternal and fetal condition in all pregnancies in which a fetal CHD is suspected. We suggest regular assessment of fetal growth and Dopplers to monitor placental function in all types of fetal CHD. Regular assessment of maternal blood pressure and PE-related symptoms should not be overlooked in these cases.

## Research implications

Placenta related complications occur in all types of CHD and also in the CHDs that cause less or no hemodynamic changes in the circulation (small VSD). Future studies on long-term neurodevelopmental outcomes should therefore include all types of CHD and not be restricted to cases that show the largest hemodynamic alterations. In addition, placenta and umbilical cord development, fetal biometry and placentally related complications like PE and PIH should be taken into account.

## Strengths

The main strength of this study is the inclusion of cases from a large regional cohort with prospective entry, in which no selection is made based on type of fetal CHD. In addition, we linked placentally related complications to fetal aortic flow and oxygenation, thereby expanding the hypothesis on the effect of aortic flow and oxygenation on placental development.

### Limitations

The first limitation of this study is the inclusion of prenatally detected CHDs only. Data on the course of the pregnancy were not available in the majority of the postnatally detected cases, as the mother or the site of the delivery could not be traced. This might have induced selection bias, as CHDs such as small ventricular septal defects and aortic arch anomalies are more frequently missed prenatally.[20] In addition, maternal characteristics, gestational age at delivery and fetal gender were not always registered. As the missing data were evenly distributed in the different groups, we do not expect any difference in results.

In addition, placenta-related complications like PE occur more often in other types of congenital anomalies as well, also in the absence of a heart defect.[30] Not all included cases underwent genetic testing. Thereby, there were differences in the type of genetic tests that were offered over the time span of the registry. Whole Exome Sequencing (WES) [31] was offered in the past five years. Though, when a syndrome was suspected during follow-up visits at the pediatric cardiology, WES was performed, as the threshold to perform WES in infancy was low. As we excluded all cases with a clinically suspected genetic diagnosis in infancy, we expect that the genetic profile of the vast majority of the included cases is normal.

## CONCLUSION

The placenta-related complications PE, PIH, FGR and IUFD are more common in pregnancies with fetal CHD. A causal relationship between these complications and the type of CHD, categorized based on fetal aortic flow and oxygenation cannot be found. This corresponds with the hypothesis that altered placental development in fetal CHD can be linked to the common early embryological developmental pathways of the placenta and the fetal heart. Ultimately, alterations in early placental development can contribute to the found PE, PIH, FGR and IUFD in pregnancies with fetal CHD.

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# SUPPORTING INFORMATION

## S1. List of primary diagnoses per group

**Extracted from:**
*Everwijn SMP, Namburete AIL, van Geloven N, Jansen FAR, Papageorghiou AT, Teunissen AK, et al. The association between flow and oxygenation and cortical development in fetuses with congenital heart defects using a brain-age prediction algorithm. Prenat Diagn. 2021;41(1):43-51.*

### Group 1. Normal flow + Low oxygenation to the brain

Oxygen-poor blood filling the aorta, with normal aortic arch flow.
Diagnoses: Transposition of the great arteries, either with or without a small ventricle septal defect.

### Group 2. Obstructed aortic flow + normal oxygenation to the brain

Biventricular heart defects, with left ventricle outflow tract obstruction, presenting with antenatal forward aortic arch flow. Some diagnoses present with small mitral valve and restricted atrial right-left shunt.
Diagnoses: Aortic valve stenosis, hypoplasia/coarctation of the aorta, interrupted aortic arch.
Shone's syndrome. Persistent left caval vein with LV inflow obstruction. Premature closure of the foramen ovale. Congenitally Corrected TGA with coarctation of the aorta.

### Group 3. Reversed aortic arch flow + mixed oxygenation to the brain

Severe aortic obstruction, presenting with antenatal reversed aortic arch flow. Univentricular heart defects.
Left-to-right shunt at atrial level (mixed blood reaches the brain through the duct and reversed aortic arch flow).
Diagnoses: HLHS. Aortic stenosis with progressive left ventricular hypoplasia. Unbalanced AVSD with aortic atresia. Congenitally Corrected TGA, RV hypoplasia with aortic arch hypoplasia.

### Group 4. Obstructed aortic arch flow + mixed oxygenation to the brain

Biventricular heart defects with abnormal connection of the great vessels and a large VSD, or univentricular heart defects, or (un)balanced AVSDs.
Intracardiac mixing occurs at atrial (a) or ventricular (v) level.
Either of above, presenting with antenatal aortic obstruction, with forward aortic arch flow (aortic arch hypoplasia, coarctatio, or aortic valve stenosis).
Postnatal intervention necessary to palliate or repair aortic obstruction.
Diagnoses: Double inlet LV (a). Tricuspid atresia (a). Complex TGA with VSD/DORV and/or ventricular hypoplasia (a/v). Unbalanced AVSD (v) with aortic obstruction.

### Group 5. Normal aortic arch flow + mixed oxygenation to the brain

Biventricular heart defects with abnormal connection of the great vessels and a large VSD, or univentricular heart defects, or (un)balanced AVSDs.Intracardiac mixing occurs at atrial (a) or ventricular (v) level.
Either of above, presenting with antenatal normal aortic calibre and flow.
Diagnoses: Absent left AV connection, DORV (a). Absent left AV connection, DORV (a). Double inlet LV (a). Tricuspid atresia (a). HRHS: pulmonary atresia or critical stenosis (a). Tetralogy of Fallot / PA with VSD / Fallot-like DORV (v). Truncus arteriosus / AP window (v). (Un)balanced AVSD (v) with normal outflow.

### Group 6. Normal aortic arch flow + normal oxygenation to the brain

Biventricular heart defects, presenting with antenatal normal aortic flow.
Diagnoses: small VSD. Ebstein's anomaly (no hydrops/normal cardiac output). Tricuspid dysplasia. Pulmonary stenosis (not critical). Absent pulmonary valve. Persistent left caval vein without LV inflow obstruction. Right aortic arch. ccTGA without additional cardiac defects. Aneurysm of the interventricular septum or cardiac diverticulum. Rhabdomyomata. Miscellaneous (scimitar, ASD, PAPVR, dextroposition).

## Abbreviations:

ASD atrioseptal defect
AV atrio-ventricular
AVSD atrio-ventricular septal defect
VSD ventricular septal defect
LV left ventricle
RV right ventricle
ccTGA congenitally corrected transposition of the great arteries
DORV double outlet right ventricle
HLHS hypoplastic left heart syndrome
HRHS hypoplastic right heart syndrome
PAPVR partially aberrant pulmonary vein return
TGA transposition of the great arteries