Adverse perinatal outcome and placental abnormalities in pregnancies with major fetal congenital heart defects: a retrospective case-control study.

Pregnancy outcomes associated with major fetal CHD

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Veronica Giorgione[1,4], Vlasta Fesslova[2], Sara Boveri[3], Massimo Candiani[1], Asma Khalil [4,5], Paolo Cavoretto[1]

1. Department of Obstetrics and Gynecology, IRCCS San Raffaele Hospital, Vita-Salute University, Milan, Italy
2. Center of Fetal Cardiology, IRCCS Policlinico San Donato, Milan, Italy
3. Scientific Directorate, IRCCS Policlinico San Donato, Milan, Italy
4. Vascular Biology Research Centre, Molecular and Clinical Sciences Research Institute, St George's University of London, London SW17 0RE, UK
5. Fetal Medicine Unit, St George's University Hospitals NHS Foundation Trust, Blackshaw Road, London SW17 0RE, UK

Corresponding author:

Vlasta Fesslova MD

Center of Fetal Cardiology, IRCCS Policlinico San Donato, Milan, Italy

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Email: cardiologiafetale.psd@grupposandonato.it

Phone: 0039 0252774511

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Ethical Background

The study followed the World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. Our retrospective study is based on a historical database where patients' data were stored anonymized.

Bulleted statements

- A possible link between congenital heart defects (CHD) and placental insufficiency has been described by previous studies.
- This study demonstrated that the risk of hypertensive disorders of pregnancy, small for gestational age babies and preterm birth is significantly higher in pregnancies with major fetal CHD.
- A pregnancy complicated by a diagnosis of fetal CHD should be monitored for hypertensive complications and preterm delivery throughout the pregnancy.

Data availability statement

Data available on request from the authors

Abstract

Objective: The placental development has been shown to be compromised in pregnancies affected by fetal congenital heart defects (CHD). This study aimed to investigate the frequency of complications related to utero-placental insufficiency in pregnancies with and without major CHD.

Method: This retrospective case-control study was conducted at a Fetal Echocardiography Center in Milan. The following outcomes were compared between the two groups: preeclampsia (PE), small for gestational age (SGA), placental disorders and preterm birth (PTB). The logistic regression analysis was adjusted for maternal age, parity, co-morbidities and mode of conception.

Results: The CHD group (n= 480) showed significantly increased incidence of PE (2.9% vs 0.9%; aOR=6.50, CI 95% 1.39-30.41, p=0.017) as compared to the control group (n=456). Placental disorders occurred more frequently in the CHD than in controls, but the increased risk showed only a borderline significance (4.5% vs 3.3%; aOR 2.56, CI 95% 0.99-1.02, p=0.046). There was a significantly higher risk of SGA in CHD than in controls (8.7% vs 3.9%; aOR: 3.37, CI 95% 1.51-7.51, p=0.003). PTB occurred in 65/477 (13.6%) cases and in 39/447 (8.7%) controls (p=0.022) (aOR 2.17, CI 95% 1.24-3.81, p=0.007).

Conclusion: Major CHD are significantly associated with the risk of PE, SGA and PTB.

Key word: preeclampsia, hypertensive disorders of pregnancy, preterm birth, uteroplacental insufficiency, fetal congenital heart defect

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Introduction

There is a growing interest in studying a possible relationship between placental abnormalities and congenital heart defects (CHD). Preterm preeclampsia (PE) is three times more common in pregnancies with fetal major CHD, and the prevalence of major CHD in pregnancies with preterm PE is also more than three times higher than in those without CHD [1]. However, published studies report controversial data on the association between impaired placentation and CHD [2]. Histological examination of the placenta in the presence of CHD has demonstrated a broad range of anomalies, including reduced absolute placental weight, a lower placental weight-to-newborn birthweight ratio and a number of vascular abnormalities such as chorangiosis, villus maturity and thrombosis [3-5]. Abnormal placental cord insertion is more common in placentas from pregnancies with fetal CHD [6,7]. Moreover, fetuses with CHD (especially within the cyanotic group) present abnormal pattern of prenatal growth with lower birth weight and head size [8].

Signs of placental dysfunction are already evident in the first trimester of pregnancy with lower serum levels of pregnancy-associated plasma protein A (PAPP-A) and

placental growth factor (PlGF) in CHD pregnancies as compared to controls [1]. Such placental impairment might be associated with underperfusion resulting in an increase in the uterine artery pulsatility index (UtA-PI) in mid-pregnancy in CHD pregnancies[2]. Compared to those without CHD, median UtA-PI is significantly higher in the pregnancies with CHD, both in pregnancies with and in those without PE.

The aim of this study was to estimate the incidence of placenta-related complications and preterm birth (PTB) in pregnancies affected by fetal CHD as compared to a control group with structurally normal fetal heart.

Materials and methods

Study population

The study was designed in compliance with the World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. An ethical approval was not required since this retrospective analysis is based on a historical database of a tertiary Fetal Echocardiography Center of Pediatric Cardiovascular Surgery at San Donato Hospital, Milan, from 2003 to May 2018. Stored data of patients who underwent fetal echocardiography were anonymized. We included singleton pregnancies with a prenatal diagnosis of major CHD and those with normal fetal hearts. Multiple pregnancies, fetuses with chromosomal abnormalities including 22q11 deletions and those which had termination of pregnancy or intrauterine fetal death were excluded. We also excluded non-structural cardiac anomalies and minor cardiac defects which do not require any particular assistance within the first year of life, such as anomalies of the fetal venous system, small interventricular muscular defects and mild anomalies of semilunar valves. We included major ventricular septal

defects (VSD) and ostium secundum atrial septal defect (ASD) only if the size of the patent foramen ovale exceeded 8 mm in the third trimester and this size was confirmed after birth. Cardiomyopathies included in the study were not familiar or metabolic and showed abnormal structural findings such as endocardial fibroelastosis, mitral dysplasia or abnormal mitral apparatus. We excluded cases in the CHD and control group that were lost to the follow-up.

We enrolled 480 pregnancies affected by major CHD and a group of 456 controls (Figure 1). The control group was chosen randomly among high-risk women who underwent fetal echocardiography for different maternal and familiar indications according to Italian guideline[9] and, as a result, they were older and with more comorbidities as showed in Table 1. Random selection of the control cohort was achieved by means of chronological matching (chronological sorting of cases and controls and choosing each case with normal heart seen after each CHD case). All subgroups of major CHD that were included are showed by Table 2. The definition of CHD was based on prenatal diagnosis by fetal cardiologist and on postnatal evaluation that was mainly used in case of discrepancy. When multiple cardiac anomalies were found, the clinically relevant diagnosis dictated the category.

The findings of this study were reported in agreement with the STROBE Statement [10].

Study outcomes

Maternal, fetal and delivery outcomes were examined including, obstetric complications, gestational age at delivery, birthweight and mode of delivery. Maternal and neonatal data collection was performed by reviewing multiple sources of medical records and recorded in an anonymized database. *Hypertensive disorders of pregnancy* (HDP) included gestational hypertension and preeclampsia (PE). Both

conditions were characterized by new-onset hypertension (≥140mm/Hg systolic or ≥90mm/Hg diastolic on two separate occasions 12 hours apart). In cases diagnosed with PE there was also maternal systemic involvement such as significant proteinuria or other signs of organ dysfunction[11]. These PE cases were analyzed separately. *Placental disorders* included placenta praevia (placenta covering the internal os or with its edge less than 20 mm from the internal os), placental abruption (separation of a normally located placenta from the uterine wall before delivery of the fetus), morbidly adherent placenta which implies an abnormal implantation of the placenta into the uterine wall (placenta accreta, increta, and percreta), and cord insertion anomalies (velamentous cord insertion and vasa praevia). The final diagnosis assigned by the obstetrician in the records at delivery was used to define the above-mentioned placental disorders. Birthweight percentiles were calculated taking into account gestational age at delivery and birthweight [12]. Neonates with birthweight less than the 10th percentile for gestational age were considered *small for gestational age* (SGA). PTB was defined when birth occurred before 37 weeks of gestation and it was divided into two types: spontaneous PTB (SPTB) when it was due to spontaneous labor and/or preterm premature rupture of membranes (pPROM), and iatrogenic PTB (IPTB) when there was a clinical indication to deliver before 37 weeks. A sub-analysis for delivery before 34 weeks was also performed.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) or median and range. Departure from normality assumption was checked by the Shapiro-Wilk test. Binary and categorical variables were presented as the numbers and percentages. Categorical variables were compared by the chi-square test or Fisher's

exact test, as appropriate, while continuous variables were analyzed using the two-sample Wilcoxon test for non-normally distributed data (Kolmogorov-Smirnov test). Dwass, Steel, Critchlow-Fligner multiple comparison procedure was used to compare two levels when the Wilcoxon test was statistically significant. Univariate logistic regression was used to explore the association between the study outcomes (categorized in HDP, PE, placental disorders, PTB and SGA) and CHD. This analysis was adjusted with other known risk factors for obstetric outcomes as the maternal age, parity, co-morbidity and type of conception.

A p-value <0.05 was considered statistically significant. The analyses were performed using SAS 9.4 (N.C., Cary, USA).

Results

The baseline characteristics of both study populations and all CHD subtypes are presented in Table 1 and 2.

HDP and PE were significantly more common in CHD group than in the control group, even after adjusting for maternal age, parity, co-morbidities and mode of conception (HDP adjusted OR 6.50, CI 95%=1.39-30.41, p=0.017; PE adjusted OR 2.62, CI 95% 1.03-6.67, p=0.036) (Table 3). PE was also significantly more frequent in tetralogy of Fallot (TOF) (4/50, 8%, p=0.004) in hypoplastic left heart syndrome (HLHS) (2/18, 11.1%, p=0.019) and in heterotaxy syndrome (2/14, 14.3%, p=0.012) than in control group (Figure 2, Table S1). Pregnancies complicated by placental disorders accounted for 4.5% and 3.3% in the CHD group and the control group, respectively (adjusted OR 2.56, CI 95% 0.99-1.02, p=0.046) (Table 3). The SGA rate was significantly higher in the CHD group than in control group (35/401, 8.7% vs 17/430, 3.9%, p=0.008) with an

adjusted OR of 3.37 (95% CI 1.51-7.51, p=0.003) (Table 3). Pregnancies affected by TOF (6/50, 12%, P=0.014), ventricular septal defect/atrial septal defect (VSD/ASD) (8/65, 12.3%, p=0.005) and cardiomyopathy (3/12, 25%, p=0.017) had significantly more SGA neonates than controls (17/430, 8.7%) (Figure 2, Table S1). However, there was no significant difference in the mean birthweight centile among the different CHD subgroups (p=0.250).

PTB before 37 weeks occurred in 65/477 (13.6%) cases and in 39/447 (8.7%) controls (p=0.022), however no statistical significance was detected for PTB before 34 weeks (cases vs controls: 2.5% vs 1.8%, p=0.451) (Table 3). PTB was significantly increased in cardiomyopathy (p=0.019), in aortic stenosis (AS) (p=0.025), in truncus arteriosus (TrA) (p=0.002) and in univentricular heart (UVH) (p=0.016) (Figure 2). When comparing the gestational age at delivery among the different subgroups of CHD, there was significant difference in the pregnancy duration. Pregnancies affected by TGA (median [IQR] 38.0 [37.6-38.6] weeks, p <0.001), and pulmonary atresia (PA) (median [IQR] 38.1 [37.7-38.6] weeks, p=0.008) ended earlier than those with VSD/ASD (median [IQR] 39.3 [37.6-40.0]). Table 4 showed the differences between spontaneous PTB and iatrogenic PTB in the CHD subtypes when compared with controls. The overall rate of SPTB and IPTB did not show significant disparity between CHD group and the control group (SPTB: 8.2% vs 5.1%, p=0.087; IPTB 4.8% vs 3.6%, p=0.414). There were significant differences in the incidence of SPTB in the pregnancies affected by TrA (p=0.003) and cardiomyopathy (p=0.025) and in the IPTB for Ebstein's/Non Ebstein's anomaly (EA) (p=0.013). Fetal cardiac interventions were performed in 3 cases: two cases of severe AS were treated by aortic valvuloplasty and one case of HLHS with restrictive atrial septum underwent atrial septostomy. Only the last case

required iatrogenic PTB at 32 weeks because of severe hydrops fetalis, the two cases of AS underwent cesarean section at 38 and 39 weeks of gestation.

Discussion

Main findings

This study showed an association between CHD and obstetric complications related to a placental impairment with a noticeable impact on maternal and neonatal outcomes. Both HDP and SGA were significantly more common in CHD compared to non-CHD control pregnancies, even after adjusting for the known risk factors for PE. The incidences of both these placenta-related complications were significantly higher in TOF, while the incidence of PE was greater in HLHS and in heterotaxy syndrome with CHD and the incidence of SGA was increased in VSD/ASD and cardiomyopathy.

Strengths and limitations

The main strength of this study is the relatively large number of pregnancies with CHD. The diagnoses of CHD were confirmed postnatally. The control group had detailed fetal heart assessment, therefore, minimizing the risk of contamination between the two study groups. All of the cases were assessed at least once by the same senior consultant providing diagnostic consistency throughout the study period (V.F.). Moreover, this allowed us to have data systematically collected for 15 years with a complete report of main fetal and maternal outcomes

The main limitations of the current study are its retrospective design and the relatively small size of each CHD subgroup, which does not allow us to draw firm conclusions in each CHD category. Elective deliveries at late preterm or at early term in the CHD

group were performed and this may have affected the incidence of some outcomes. The prevalence of HDP, for instance, could be reduced due to a competing of risk between delivery and some outcomes. It is crucial to underline how this competitive mechanism may also explain the low incidence of negative outcomes in our high-risk control group[13]. Indeed, another limitation of the study is that the control group does not represent the normal population. Therefore, it is likely that "precious" pregnancies in older patients were managed actively in terms of delivery as demonstrated by a similar gestational age at delivery between the two groups. These high-risk patients might have taken aspirin more often than CHD group with the subsequent prevention of preterm PE[14]. However, we cannot confirm this hypothesis because information on aspirin usage was not available in both groups. Similarly, it was not possible to distinguish babies who were constitutionally small from those who were fetal growth restricted due to a utero-placental insufficiency or a genetic syndrome that cannot be detected by a karyotype analysis.

Despite these limitations, this study provides evidence that CHD pregnancies presented a higher risk of developing placenta-related complications, such as HDP and SGA, compared to a control group of high-risk pregnant patients after adjusting for known risk factors for utero-placental insufficiency.

Interpretation

Both microscopic, as well as macroscopic, anomalies are more commonly seen in the placentas retrieved from pregnancies with CHD [3-7]. Moreover, first-trimester markers of placental function such as PAPP-A and PlGF have been found to be lower in CHD pregnancies than in matched pregnancies with structurally normal hearts suggesting

that in isolated CHD there is a placental dysfunction which is already established from the first trimester [1,2,15,16]. However, imbalances in placental angiogenic factors (sFLT and PlGF) have been found to be shown in pregnancies without known placental dysfunction reflecting perhaps the common origin of the heart and placenta[15]. Besides these placental morpho-functional aspects, previous studies have outlined that PE was more frequent in pregnancies affected by fetal CHD [17,18]. In a registry-based study on 18038 pregnancies, Boyed et al. reported that fetal CHD increases the risk of early preeclampsia by 7-fold in the current pregnancy and by 2- to 3-fold in a subsequent pregnancy. Therefore, they proposed a possible link between preterm PE and inborn cardiac defects hypothesizing a possible maternal cause that put both the mother and her fetuses at risk for both conditions [17].

The perinatal mortality and morbidity of newborns suffering from CHD decrease as the gestational age approaches 40 weeks [19,20]. The five-year survival of CHD children is adversely influenced by preterm delivery and lower birthweight [21]. Our data confirms a significant increase in the risk of PTB before 37 weeks, after adjusting for maternal factors. A similar trend was observed for PTB before 34 weeks, but it did not reach a statistical significance that could be explained by the small numbers of patients. PTB occurred more frequently in some CHD subgroups, such as TOF, EA, AVSD, AS, UVH and TrA. Among these, UVH and TrA experienced SPTB more often than controls, whereas preterm birth of the fetuses with PA and EA was caused more frequently by iatrogenic decisions when compared with controls.

We observed that CHD pregnancies presented an increased risk of SPTB compared with controls and for this reason they should be monitored in order to detect possible causes of PTB. On the other hand, IPTB needs to be weighed against its indications. It

is likely that in most cases, IPTB is a trade-off outcome with severe fetal compromise of even fetal death and future research should focus on assessment of these components and their imbalance. Laas et al. also found out a significant association of SPTB in newborns with CHD [22]. A possible role of placental dysfunction has been proposed in the explanation of SPTB [23]. The lack of physiological transformation of spiral uterine arteries was found in the placentas and in the uterine placental bed biopsies of women with SPTB or pPROM. Moreover, it has been shown that, after SPTB, histological placenta lesions due to placental malperfusion were more common as compared to those secondary to inflammation/infection [24]. However, the mechanism by which placental dysfunction activates the onset of labor is still speculative and it is extremely likely that multiple factors are involved.

Interestingly, new increasing evidence has revealed that both surgical outcome and neonatal brain development of CHD might be influenced by the intra-uterine environment and placental impairment [25,26]. This aspect underlines the urgency in preventing these conditions in order to improve the overall neonatal outcome of CHD.

It is possible to speculate that the observed placental insufficiency might be caused by unidentified maternal factors, which are associated with fetal CHD and with the subsequent development of obstetric complications[27]. Such hypothesis is suggested by the fact that CHD are more common in pregnancies with a well-known placental impairment, such as pregnancies conceived via assisted conception [28], and by the common embryological origin of the heart and placenta from the mesoderm [29].

Conclusion

The risk of PE, HDP and SGA is significantly higher in pregnancies with major fetal CHD.

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Table 1. Characteristics of the two study populations

	Major CHD (n=480)	**Controls (n=456)**	**p-value**
Maternal age in years, median (IQR)	32.0 (29.0-36.0)	36.0 (33.0-39.0)	**<0.0001**
Nulliparous, n (%)	310 (64.9)	306 (67.3)	0.439
Spontaneous conception, n (%)	462 (97.1)	239 (65.4)	**<0.0001**
Maternal medical history:			
Maternal pre- and gestational diabetes, n (%)	15 (3.1)	10 (2.2)	0.484
Maternal infections (parvovirus, CMV), n (%)	5 (1.0)	-	0.125
Maternal autoimmune disease, n (%)	6 (1.3)	44 (9.7)	**<0.0001**
Maternal hypertension, n (%)	2 (0.4)	4 (0.9)	0.056
Others (migraine, epilepsy, mental health disorders and dysthyroidism)	14 (2.9)	27 (5.9)	**0.025**
Mode of delivery, n (%)			
Vaginal birth	129 (27.3)	229 (51.1)	**<0.0001**
Vaginal birth following induction of labour	80 (16.9)	24 (5.4)	**<0.0001**
Cesarean section	243 (51.4)	176 (39.3)	**<0.0001**
Cesarean section following induction of labour	21 (4.4)	19 (4.2)	0.568
Gestational age at delivery in weeks, median (IQR)	38.0 (27.0-39.0)	38.0 (38.0-40.0)	0.627
Birthweight centile, median (IQR)	39.3 (24.8-56.5)	46.3 (30.4-63.5)	**<0.0001**
Hydrops fetalis, n (%)	4 (0.8)	0	**-**

Table 2. Subgroups of major congenital heart defects

CHD subgroup	N (%)
Transposition of great arteries	74 (15.4)
Pulmonary stenosis	23 (4.8)
Atrioventricular septal defect	22 (4.6)
Ventricular/Atrial Septal defects	65 (13.5)
Cardiomyopathy	12 (2.5)
Tetralogy of Fallot	50 (10.5)
Ebstein's/Non Ebstein's anomaly	23 (4.8)
Coarctation of aorta/ Interrupted aortic arch	51 (10.6)
Tricuspid atresia	17 (3.5)
Hypoplastic left heart syndrome	18 (3.8)
Aortic stenosis	19 (4.0)
Truncus arteriosus	7 (1.5)
Double outlet right ventricle	18 (3.8)
Pulmonary atresia with intact ventricular septum	30 (6.3)
Univentricular heart	18 (3.8)
Heterotaxy syndrome with CHD	14 (2.9)
Other (double aortic arch, left ventricular aneurysm, congenitally corrected transposition of great arteries, total anomalous pulmonary venous returns)	19 (4.0)
Total	480 (100)

Table 3. Placenta-related complications in the two study populations

Obstetrical complications	**Major CHD (n=480)**	**Controls (n=456)**	**Odds ratio (95% CI)†**	**p-value**	**Adjusted odds ratio (95% CI)†**	***p* value**
Hypertensive disorder of pregnancies, n (%)	21/480 (4.3)	15/456 (3.3)	1.35 (0.69-2.64)	0.391	6.50 (1.39-30.41)	**0.017**
Preeclampsia, n (%)	14/480 (2.9)	4/456 (0.9)	3.39 (1.11-10.39)	**0.032**	2.62 (1.03-6.67)	**0.036**
Placental disorders, n (%)	22/480 (4.5)	15/456 (3.3)	1.41 (0.72-2.76)	0.312	2.56 (0.99-1.02)	**0.046**
Preterm birth <37 weeks, n (%)	65/477 (13.6)	39/447 (8.7)	1.65 (1.09-2.51)	**0.019**	2.17 (1.24-3.81)	**0.007**
Preterm birth <34 weeks, n (%)	12/477 (2.5)	9/447 (1.8)	1.42 (0.57-3.50)	0.451	2.93 (0.80-10.82)	0.106
Small for gestational age, n (%)	35/401 (8.7)	17/430 (3.9)	2.21 (1.22-4.00)	**0.009**	3.37 (1.51-7.51)	**0.003**

†Adjusted for maternal age, parity, co-morbidities and mode of conception

Table 4. The frequency of spontaneous and iatrogenic preterm birth in each subgroup of major cardiac heart defects in comparison to control group

Major congenital heart disease	Total	SPTB	p-value	IPTB	p-value
Transposition of great arteries, n (%)	74	6 (8.1)	0.280	2 (2.7)	1.00
Pulmonary stenosis, n (%)	23	2 (8.7)	0.350	-	-
Atrioventricular septal defect, n (%)	22	3 (13.6)	0.115	1 (4.6)	0.565
Ventricular/Atrial Septal defects, n (%)	64	3 (4.7)	1.00	3 (4.7)	0.720
Cardiomyopathy, n (%)	12	3 (25.0)	**0.025**	1 (8.3)	0.368
Tetralogy of Fallot, n (%)	49	5 (10.2)	0.181	2 (4.1)	0.695
Ebstein's/Non Ebstein's anomaly, n (%)	23	1 (4.4)	1.00	4 (17.4)	**0.013**
Coarctation of aorta/ Interrupted aortic arch, n (%)	51	1 (2.0)	0.500	-	-
Tricuspid atresia, n (%)	17	-	-	-	-
Hypoplastic left heart syndrome, n (%)	18	1 (5.6)	1.00	2 (11.1)	0.150
Aortic stenosis, n (%)	19	3 (15.8)	0.082	2 (10.5)	0.163
Truncus arteriosus, n (%)	7	4 (57.1)	**<0.001**	-	-
Double outlet right ventricle, n (%)	18	2 (11.1)	0.251	-	-
Pulmonary atresia, n (%)	30	-	-	3 (10.0)	0.110
Univentricular heart, n (%)	17	3 (17.7)	0.063	2 (11.8)	0.137
Heterotaxy syndrome with CHD, n (%)	14	1 (7.1)	0.532	-	-
Other, n (%)	19	1 (5.3)	1.00	1 (5.3)	0.513
Total, n (%)	477	39 (8.2)	0.087	23 (4.8)	0.414

List of the abbreviations: SPTB= spontaneous preterm birth, IPTB= iatrogenic preterm birth, CHD= congenital heart defects

Figure legends

Figure 1. Flow chart of study design.

List of the abbreviations: CHD=congenital heart defects, TOP=termination of pregnancy, IUFD=intrauterine fetal death

Figure 2. Placenta-related complications in each subgroup of major congenital heart defects in comparison to control group. * p value < 0.05

List of the abbreviations: PE= preeclampsia, PD= placental disorders, PTB=preterm birth<37, SGA=small for gestational age, TGA=Transposition of great arteries, PS=Pulmonary stenosis, AVSD= Atrioventricular septal defect, VSD/ASD=Ventricular/Atrial Septal defects, CMP= Cardiomyopathy, TOF= Tetralogy of Fallot, EA= Ebstein's/Non Ebstein's anomaly, CoA/IAA= Coarctation of aorta/ Interrupted aortic arch, TA=Tricuspid atresia, HLHS= Hypoplastic left heart syndrome, AS= Aortic stenosis, TrA= Truncus arteriosus, DORV= Double outlet right ventricle, PA= Pulmonary atresia, UVH= Univentricular heart, Heterotaxy= Heterotaxy syndrome with CHD