Review Article

Evaluation of Prenatal Diagnosis of Congenital Heart Diseases: Accuracy of Fetal Echocardiography and Postnatal Outcome from a Regional Experience

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Abstract

***Introduction**: Prenatal diagnosis has a strong impact on therapeutic terminations of pregnancy and prevalence of Congenital Heart Diseases (CHD) in live births.*

***Objective**: To evaluate the impact of prenatal echocardiographic diagnosis of CHD analyzing pregnancy outcomes and postnatal mortality, and assess fetal echocardiography accuracy.*

***Design**: A retrospective cohort study.*

***Setting**: Mediterranean Pediatric Cardiology Center, Taormina, and Garibaldi Hospital, Catania, Italy.*

***Population**: From January 2016 to December 2019, 2495 echocardiographs were performed in pregnant women sent to our attention for morphofunctional fetal cardiac evaluation and a total of 439 cases of CHD were diagnosed.*

***Methods**: Fetal echocardiography allowed to define cardiac anatomy and fetal rhythm, to monitor pregnancy conduction, to plan intrauterine therapeutic measures, pharmacological (treatment of fetal arrhythmias) or interventional (percutaneous fetal valvuloplasty), and finally cares in the post-natal period.*

***Results**: The termination of pregnancy (TOP) was practiced in 16.6% of the pathological fetuses, of whom 22% were associated with chromosomal and/or extracardiac abnormalities. No cases of intrauterine death were recorded. CHD diagnoses were divided into 6 groups to anatomical cardiac malformation and type of surgical or percutaneous treatment. The first group including heart disease susceptible only to Fontan-type palliative surgery was affected by a major number of TOP (47% of all TOP). A total of 306 patients were alive during the period study, twenty-five pregnancies have not been followed in our center, 16.4% pregnants decided for TOP and 40 patients died afterbirths. Kaplan-Meyer curves showed higher mortality in the first and third groups. Prenatal diagnostic accuracy was about 94% and discordant diagnosis (comparing pre and post-natal) was 10%, of which 31% required a variation on therapeutic strategy.*

***Conclusion**: Fetal echocardiography diagnosis of CHD affected pregnancy outcomes in terms of TOP and therapeutic strategy in case of arrhythmia; the prenatal diagnostic accuracy was high as only in 10% of patients there was a discrepancy between prenatal and postnatal diagnosis.*

***Keywords:** Fetal echocardiography - congenital heart disease - prenatal diagnosis – termination of pregnancy.*

Introduction

Prenatal diagnosis of congenital heart disease (CHD) allowed reduction significantly perinatal morbidity and mortality. The development of new ultrasound technologies and above all the greater experience of the operator permitted us to achieve excellent levels of accuracy in prenatal echocardiography diagnosis and to plan the best therapeutic strategy as well as the delivery in a third-level hospital equipped with cardiac surgery and neonatal intensive care.

The great interest surrounding the prenatal diagnosis of cardiac defects is justified by the epidemiological relevance of the problem, since the incidence is 1% on all live births [1], a potentially even greater percentage if we consider spontaneous abortions and stillbirths.

In Europe, a prevalence of CHD is estimated at 7.2 children per 1,000 live births and 8 per 1,000 considering TOP and fetal deaths [2]. Among premature births, excluding the patency of the ductus arteriosous and atrial septal defects, it reaches 12.5 per 1000 live births [3]. CHD is the major cause of infant mortality, about 3% of all infant deaths and 46% of deaths due to congenital malformations.

CHD represent the main cause of infant death in the western world [4].

Prenatal diagnosis has a strong impact on therapeutic terminations of pregnancy (TOP) and on reducing the prevalence of CHD in live births. A recent analysis [5] evaluated international trends (Europe, America and Asia) on prenatal diagnosis of complex cardiac anomalies and found considerable variability in the prenatal diagnosis rate of heart disease ranging from 13% to 87%. Therefore, the purpose of this study is to analyze the impact of the prenatal echocardiographic diagnosis on our regional population and the outcome of the pregnancy and treatment at birth.

About 18-25% of affected children in natural history die within the first year of life, while 4% of survived do not exceed 16 years [6]. Overall, the CHD is distributed homogeneously in the two genders (males 48.7%, females 51.3%) [7], while there is a different incidence of some specific heart diseases between various ethnic groups. Furthermore, it has been shown that CHD is more frequent in fetuses of twin pregnancies than in single pregnancies [8].

According to a recent meta-analysis [9] in the context of CHD, someone is decidedly more frequent than others, such as ventricular septal defect (VSD), atrial septal defect (ASD), patent ductus arteriosous (PDA), pulmonary stenosis (PS), tetralogy of Fallot (TOF) and transposition of great arteries (TGA). The trend of CHD, without considering septal defects, shows a progressive increase over time with an almost doubled prevalence of obstructions in the right ventricular outflow tract (RVOT) and a reduction of about

one third in obstructions in the left ventricular outflow tract (LVOT), probably related to increased TOP due to the diagnosis of CHD such as hypoplastic left ventricular syndrome (HLHS). However, these data are influenced by multiple variables: method of assessment, method of diagnosis, population studied, subjects examined, verification of the diagnosis even after birth, assessment period, inclusion and exclusion criteria, type of classification [10].

Material

We retrospectively analyzed data collected in the Mediterranean Pediatric Cardiological Center (MPCC) and the Pediatric Cardiology Unit of Garibaldi Nesima Hospital (GNH) in the period from 1 January 2016 to 31 December 2019. The team of pediatric cardiologists performed prenatal diagnosis and counseling, medical treatment (in fetal arrhythmias) and follow-up of pregnancy collaborating with the pediatric cardiac surgeons, anesthesiologists, and gynecologists. A total of 2495 fetal echocardiography were performed in 4 years (1920 at MPCC, 575 at GNH*).* The pregnant women sent to our centers for fetal echocardiography had the following maternal or fetal risk factors:

Maternal risk factors:

• first-degree family history of CHD or chromosomal/genetic abnormalities,

• endocrine pathology (diabetes, dystyroidism),

• rheumatological pathology (presence of anti-Ro / SSA, anti-Ro / SSB),

• infections during pregnancy,

• teratogenic drugs;

Fetal risk factors:

• congenital extracardiac malformation,

• suspicion of heart diseases or rhythm disturbances,

• abnormalities of amniotic fluid (oligo-polyhydramnios),

• non-immune hydrops,

• intrauterine fetal growth retardation,

• chromosomal and extrachromosomal abnormalities.

The majority of pregnants were referred after the first gynecological screening, or from other specialists such as geneticists, cardiologists, or rheumatologists.

The gestational age (GA) varied from 15 to 40 weeks (w) [mean 24 w, min 13 w, max 40 w] of pregnancy. The pregnant women were then followed up from 1 to a maximum of 7 controls, according to the problem encountered.

A total of 439 (17.5%) prenatal diagnosis of CHD were performed considering both anatomical malformations and rhythm disorders; data collected were analyzed in terms of conduction of pregnancy and neonatal outcome. CHD were divided into 6 groups according to the anatomical type and the morbidity and mortality of the cardiac disease (Table 1).

Table 1. CHD divided in 6 groups according to severity of anatomical malformations and mortality.

GROUP	DEFINITION	HEART DISEASE
1	Severe CHD treated with palliative surgery	HLHS, univentricular heart, heterotaxy
2	CHD with high morbilità and mortality at birth needing early surgical therapy	Transposition of great arteries
3	CHD needs surgical or interventional treatment after birth	Conotruncal anomalies (tetralogy of Fallot, pulmonary atresia and VSD, truncus arteriosous, double outlet right ventricle),Large VSD, Atrio-ventricular defect, Aortic Coarctation and VSD
4	CHD needs postnatal follow-up	Aortic stenosis, Aortic Coartation, Pulmonary stenosis, Ebstein anomlay, Small VSD, Cardiomyophaty, Cardiac tumor.
5	CHD without impact on outcome	Muscolar VSD,Systemic venous anomalies
6	Arrhythmias	SVEB, VEB, SVT, AVB, Atrial Flutter

AVB: atrioventricular block, CHD: congenital heart disease, HLHS: hypoplasic left heart syndrome, SVEB: supraventricular ectopic beats, SVT: supraventricular tachycardia, VEB: ventricular ectopic beats, VSD: ventricula septal defect.

The data relating to the pregnancy follow-up were obtained by outpatient reports, echocardiographic examination at birth, telephone follow-up (if the birth had been carried out in another structure) and necropsy reports in case of TOP. No cases of intrauterine death were recorded.

The accuracy of the diagnosis was verified by comparing the pre and postnatal echocardiographic reports, the anatomy-surgical diagnosis and anatomopathological reports.

Methods

The main application of fetal echocardiography was the description of cardiac anatomy and fetal rhythm, monitoring of pregnancy conduction, planning of the consequent intrauterine therapeutic measures, both pharmacological (treatment of fetal arrhythmias) and interventional (percutaneous fetal valvuloplasty) and finally the planning of care in the post-natal period.

In our study, a Philips iE33 echocardiography with an 8 MHz probe was used for the fetal echocardiographic examination. The examination was performed transabdominally with the pregnant woman in the supine position and/or in left lateral semi-decubitus. For the morphological study, the fetal heart was examined using a two-dimensional technique, with Doppler and color Doppler, in the various sections obtainable on the longitudinal and transverse planes (long axis, short axis, four chambers view, outflows).

The cardiac structures, the dynamics of the atrioventricular (AV) and semilunar valve structures were thus recognized: a rational diagnostic approach was followed consisting first in the anatomical identification of the cardiac segments and subsequently in their sequential connection, a sequential approach that let to recognize almost of the entire malformation spectrum of CHD. The ventricular function, the size of the heart chambers, the septal thicknesses, and the walls of the ventricles were studied using a one-dimensional technique.

One-dimensional echocardiography and pulsed Doppler (PW) were used to evaluate the rhythm disturbances; the heart rate was determined by positioning the Doppler on the outflows of the great arteries and calculating the interval between two waves of ventricular systole and the mechanical PR by

positioning the Doppler on the mitro-aortic junction and calculating the interval between the mitral A wave and the beginning of the ventricular systole wave.

Statistical Analysis

The SPSS 26 program was used for the statistical analysis, the population studied was divided into numerical variables (year, age, gestational period, timing) and categorical (previous pregnancies, previous abortions, family history, diabetes gestation, infections, autoimmune diseases, teratogenic therapy, extracardiac malformations, fetal heart disease, TOP, correct, incomplete or similar fetal diagnosis, death). Synthetic and variability indicators and prevalence were calculated from the variables.

The x2 test was used to evaluate the association between two variables and their significance. Survival was described with Kaplan Meier curves.

We considered with a separate analysis the population of group 1, evaluating the impact of prenatal diagnosis on the incidence of TOP and postnatal mortality.

Results

Population

In four years have been performed a total of 2495 prenatal echocardiography exams, a mean of 550 per year (480 at the MPCC, 70 at the GNH) with a maximum of 634 in 2018 and a minimum of 494 in 2019; the prevalence of CHD was 17,5 % relatively constant over the study period.

Most of the fetal echocardiography exams (67%) were requested by gynecologists; the others from rheumatologists, geneticists and cardiologists.

The indications for fetal echocardiography were suspected heart diseases, maternal diseases, chromosomal or extracardiac anomalies, family history of CHD or fetal risk factors (table 2). The main indication for which pregnant women were sent to our observation was the suspicion of CHD, which alone constitutes 61.4% of examination requests.

Table 2. Indications for fetal echocardiography.

INDICATION		**%**
Heart disease	Arrhythmic disorder Anatomical disorder	61%
Maternal disease	Diabetes Drugs in pregnancy Connective tissue disease Infections Previous abortions	28%
Chromosomic and extracardiac diseases	Chromosomal anomalies Diaphragmatic ernia Duodenal and esophageal atresia Gastroschisis/omphalocele Singular umbilical artery	9%
Family history		6,4%
Fetal risk	Twins Amiotic fluid abnormalities Low growth Increased nuchal translucency	2%

CHD was diagnosed on 439 of 2495 fetal echocardiography with a prevalence of 17.5%. The mean GA at the time of the first diagnosis was 24.3 w (min 13 w, max 40 w, median 23 w); less than 24 GA in 262 patients (60%) and greater than 24 GA in 174 (40%).

The mean age of the pregnant examined with pathological fetus was 31.7 years (min 14 years, max 49 years). Among all examined pregnancies, 264 (60%) were multiparous, 9 (2%) were twins, and of these one was triplets. About 20% of pregnant women had a history of holy abortion, so we analyzed whether this data could have an impact on the incidence of CHD. Our results showed that this factor was present between 20 and 25% in groups 1 - 3 - 4, and around 10% in the remaining groups. Then there wasn't a correlation (p 0.08) between polyabortivity and the anatomical type of CHD.

Table 3. Clinical parameters.

CLINICAL PARAMETERS	TOT (N= 434)
Age, years ±DS	31,7 ± 6,2
Previous pregnancies, n (%)	264 (60,8)
Twins, n (%)	9 (2,1)
Previous abortions, n (%)	89 (20,5)
Family history for CHD, n (%)	28 (6,4)
Gestational diabetes, n (%)	5 (1,1)
Infections, n (%)	6 (1,4)
Autoimmune diseases, n (%)	20 (4,6)
Drugs, n (%)	2 (0,5)
Extracardiac anomalies, n (%)	38 (8,7)
Trisomy 21, n (%)	7 (1,6)
Trisomy 18, n (%)	2 (0,5)
GA at first diagnosis, week ±DS	24 ± 5,7

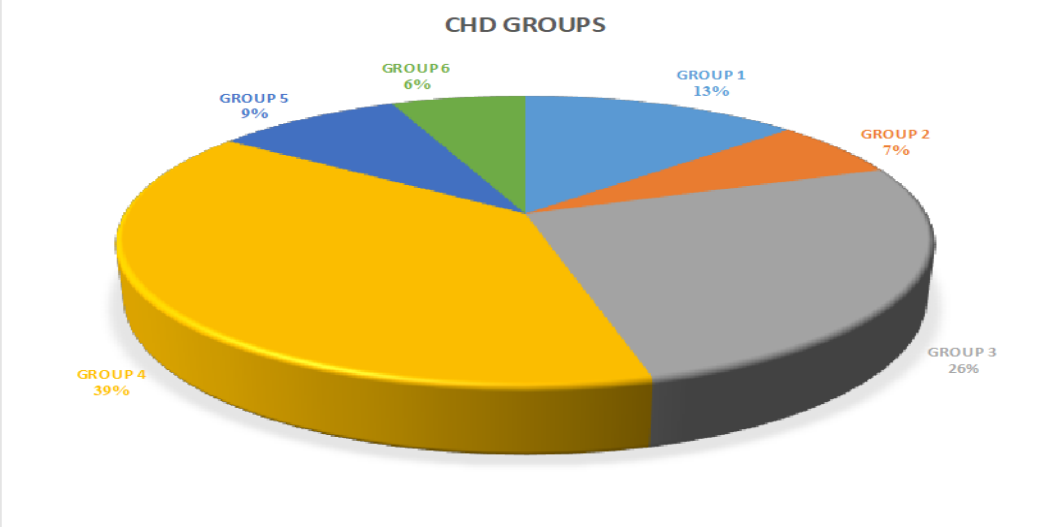
Family history of CHD was present in 28 women (6,4%), among groups it was more frequent in group 3 (7,9 %), but without an incidence statistically significative (p 0,7).

Maternal diseases were present in 20 pregnants (4.5%), the most frequent was Hashimoto thyroiditis but there's not a cause-effect correlation between autoimmune thyroiditis and CHD. It was more frequent because is the most common endocrinopathy wide in women.

Fetal chromosomal anomalies were present in 12 (2.7%) cases (5 cases of AVD and 1 of VSD associated to 21 trisomy, 3 cases of VSD associated to 18 trisomies, and 3 cases of truncus arteriosous associated with respectively Oliver-Adams S., Di George S. and chromosomal imbalance).

Fetal extracardiac anomalies were diagnosed in 38 (8.7%) pregnant women and the most common were polyhydramnios, unique umbilical artery, radius agenesis, omphalocele, diaphragmatic hernia, cleft lip and palate, and intestinal abnormalities.

Among overall fetal echocardiographic exams were diagnosed 439 CHD divided into 6 groups as in the graph. 1.



Graphic 1. Total fetal diagnoses and their frequency

The largest group is the fourth (38.9%) including cardiac malformations that require post-natal follow-up (aortic stenosis, isolated aortic coarctation, pulmonary stenosis, Ebstein's anomaly, perimembranous VSD, cardiomyopathies, cardiac tumors); the group 3 (conotruncal anomalies, malalignment VSD, inlet VSD, atrioventricular defects, aortic coarctation with VSD) accounts 26.2% of diagnosis, the group 1 (univentricular heart, HLHS, heterotaxy S.) accounts 13.2% of cardiac malformations, the group 5 (muscle VSD, venous return anomalies) 9%, the group 2 (TGA) 7% and group 6 (arrhythmias) 6.4% (Graph. 1, Table 4).

Table 4. Diagnosis of CHD.

GROUP	DIAGNOSIS	N	%
1	HLHS	33	7.5
1	UNIVENTRICULAR HEART	18	4.1
1	HETEROTAXY	8	1.8

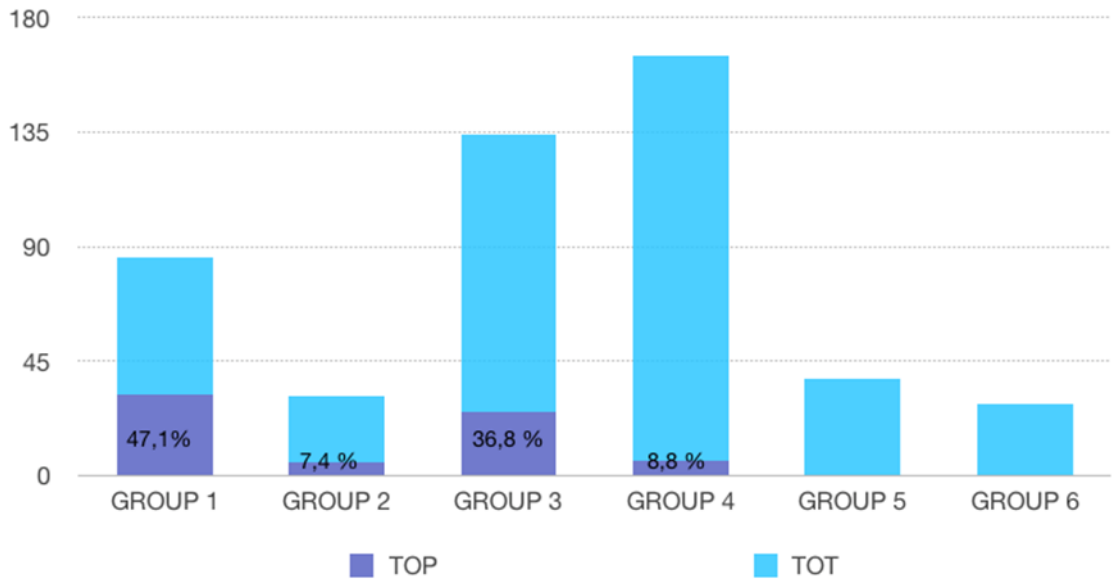
2	TGA	16	3.6
2	TGA + VSD	8	1.8
2	CCTGA	4	0.4
3	TOF	20	4.5
3	DORV	15	3.4
3	TRUNCUS	9	2
3	PA + VSD	8	1.8
3	PAIS	2	0.4
3	MALALIGNMENT VSD	6	1.3
3	INLET VSD	4	0.4
3	AVD	30	6.8
3	CoA/HYPOPLASIC ARCH + VSD	21	4.7
4	AS	7	1.6
4	CoA	72	16.4
4	PS/PA	19	4.3
4	EBSTEIN	8	1.8
4	PERIMEMBRANOUS VSD	5	1.1
4	COR TRIATRIATUM	5	1.1
4	ARCH ANOMALIES	31	7
4	CARDIOMYOPHATY	8	1.8
4	CARDIAC TUMORS	12	2.7
5	SYSTEMIC ANOMALOUS VENOUS RETURNS	19	4.3
5	MUSCOLAR VSD	20	4.5
6	ARRHYTHMIAS	28	6.4

AS: aortic stenosis, AVD: atrioventricular defect, CCTGA: congenital corrected transposition of great arteries, COA: aortic coarctation, DORV: double outlet right ventricle, HLHS: hypoplasic left heart syndrome, PA: pulmonary atresia, PAIS: pulmonary atresia with intact septum, PS: pulmonary stenosis, TGA: transposition of great arteries, TOF: tetralogy of Fallot, VSD: ventricular septal defect. Arch anomalies: double aortic arch, hypoplasic arch, vascular ring.

Conducting pregnancy and postnatal outcome

I) Termination of pregnancy

Among 439 pregnant women, 25 (5.6%) were lost to follow up and 68 (16.4%) decided for TOP. Of all TOP about half (47.1%) were performed by pregnant women whose diagnosis of CHD belonged to group 1, 36.8% to group 3, 8.8% to group 4 and 7.4% to group 2 (Graph 2). No TOP was performed in groups 5 and 6.



Graphic 2. Incidence of TOP in each group.

Chromosomal and extracardiac anomalies were present in 22% (15/68) of all TOP (7 in group 1, 1 in group 2, 5 in group 3 and 2 in group 4).

Analyzing the influence that chromosomal disorders and extracardiac malformations had in association with CHD, we found that there was a statistically significant impact on the decision to TOP ($p < 0.001$), as well as in pregnancies leading full term was recorded high mortality equal to 15% of all deaths (6 of 40, $p < 0.012$).

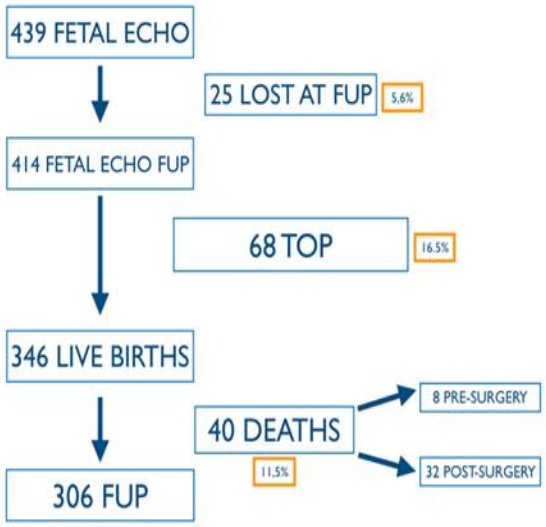
II) Pharmacological Intrauterine Therapy

In all of our series, rhythm disturbances were diagnosed in 28 fetuses: 9 (32.1%) cases of supraventricular tachyarrhythmias (SVT), 2 (7.1%) of the atrioventricular block (AVB) and 17 (60.8%) of SVEB.

Four (14.3%) of the 9 fetuses with tachyarrhythmia were treated through maternal oral drugs (amiodarone if hydrops was present, or flecainide). If GA was > 32 weeks and fetal arrhythmia persisted with heart failure signs or in case of twin pregnancy, cesarean section was performed to treat directly the newborn at birth.

In the fetal AVB, the pregnant women were followed with close echocardiographic monitoring of fetal HR until delivery. In one case the pregnant woman was affected by S. Sjogren (Anti-Ro SSA) and the fetus presented a complete AVB treated through dexamethasone per os, and at birth, the patient underwent pacemaker implantation in the neonatal period.

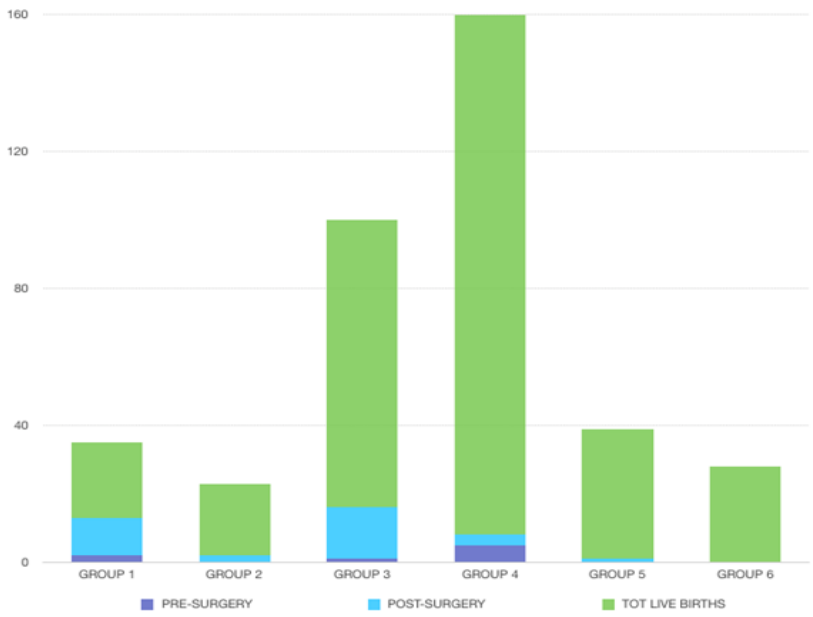
III) Outcome and follow-up of births



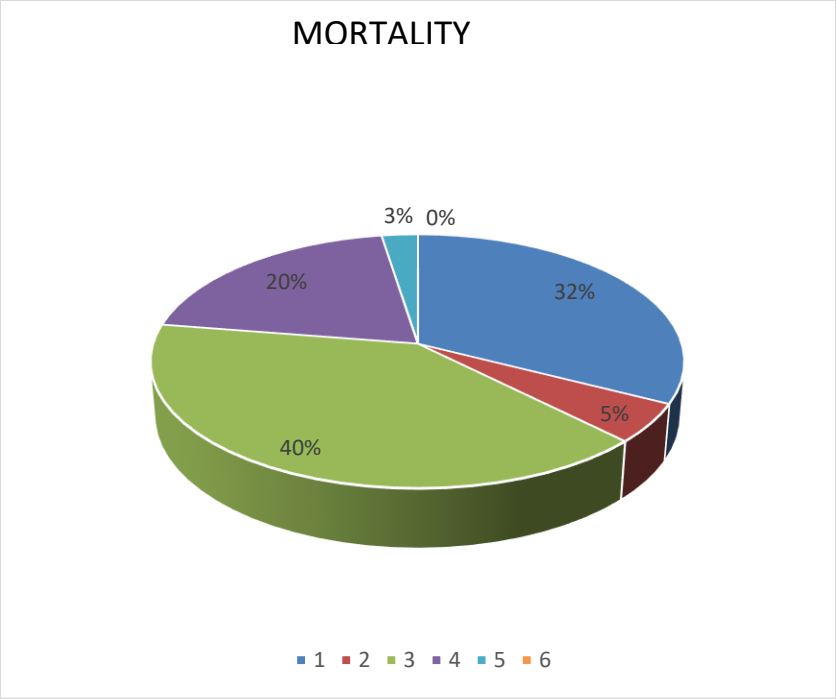
Graphic 3. Outcome in the population studied.

Of 439 women with heart disease initially identified, 25 (5.6%) were lost to follow-up, 68 (15.4%) decided for TOP and 346 pregnancies (78.6%) arrived full term. Three hundred and six patients (69.4%) were alive at the time of the last follow-up. Forty (11.5%) died during the study period (Graph. 3).

Mortality after birth accounts for 40 patients of whom 8 (20%) died before surgical treatment (prematurity, diaphragmatic ernia, trisomy 18, aortic stenosis (n. 2), ventricular dysfunction, pulmonary atresia and ventricular septal defect, HLHS) and the others after at least the first cardiac surgery (Graph 4-5).

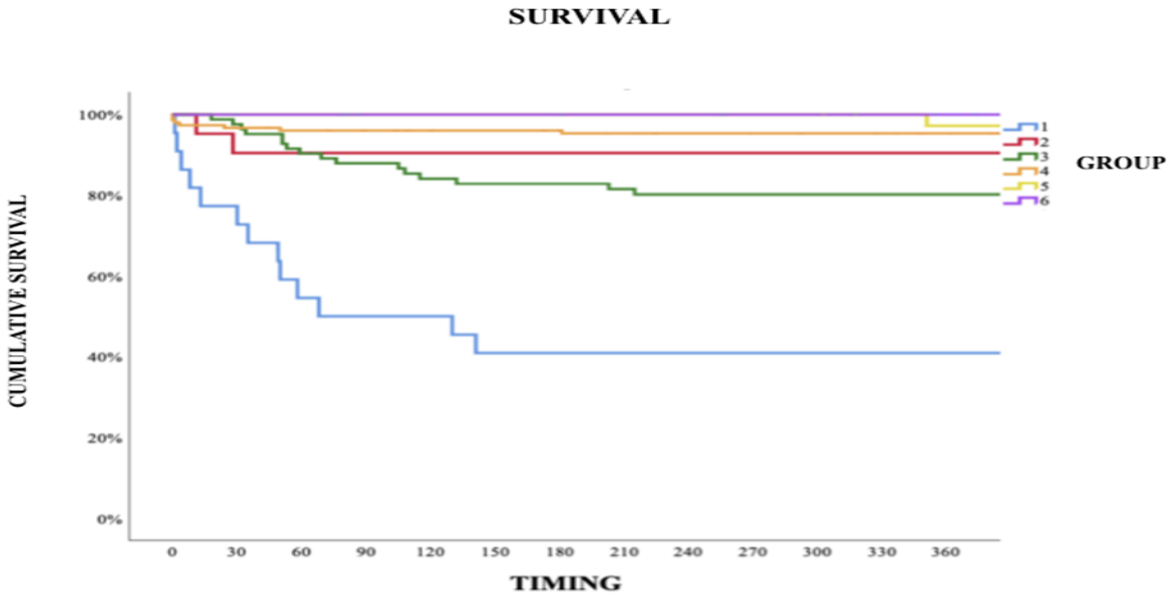


Graphic 4. Mortality pre and post surgery.



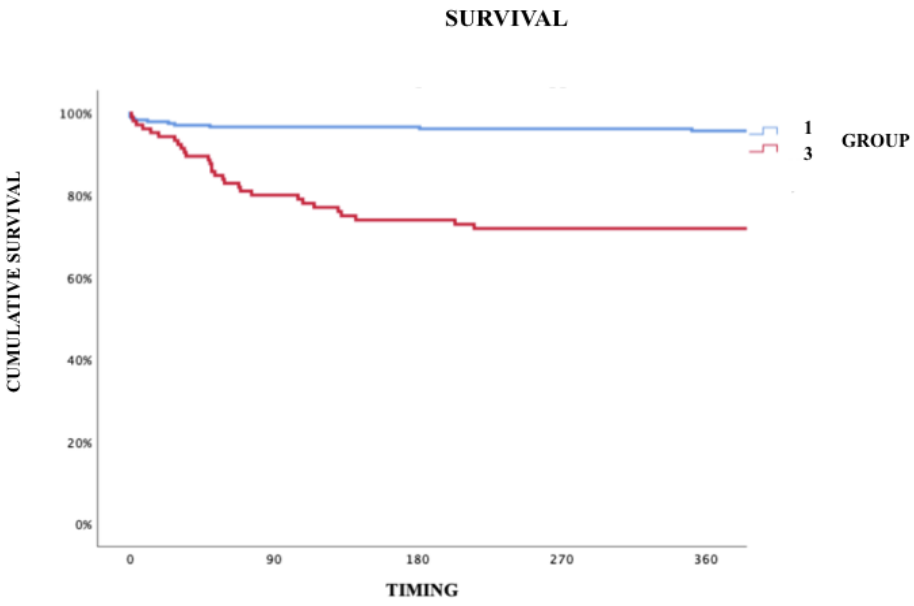
Graphic 5 - Mortality for each group.

Cumulatively 40% (n.15) of all deaths involved in group 3, 32% (n.11) occurred in patients of group 1; the remaining 28% concerns groups 2-4-5, while no deaths were recorded in arrhythmic patients.



Gruppo 1	21	16	12	9	9
Gruppo 2	20	19	18	16	12
Gruppo 3	82	81	72	62	50
Gruppo 4	151	146	142	137	122
Gruppo 5	37	37	37	37	34
Gruppo 6	28	28	28	28	28

Graphic 6. Kaplan-Meier curves.



Gruppo 1	21	12	9	9
Gruppo 3	82	72	62	50

Graphic 7. Kaplan-Meier curves for group 1 and 3.

From the Kaplan-Meier curves (Graph. 6) elaborated for every single group, it is confirmed that there is statistically significant mortality ($p < 0.001$) in the group 1 and 3. Comparing the latter two groups with the highest mortality emerged a significant statistical difference ($p < 0.01$). Therefore, excluding group 1, as the Kaplan-Meier curve (Graph. 7) deviated excessively from the others, and comparing group 3, which showed lower survival than the others, with group 6, with the survival of 100%, not statistical significance was demonstrated. It confirmed that the only group with high mortality remains the group of cardiopathies with univentricular heart, as confirmed in the literature [11].

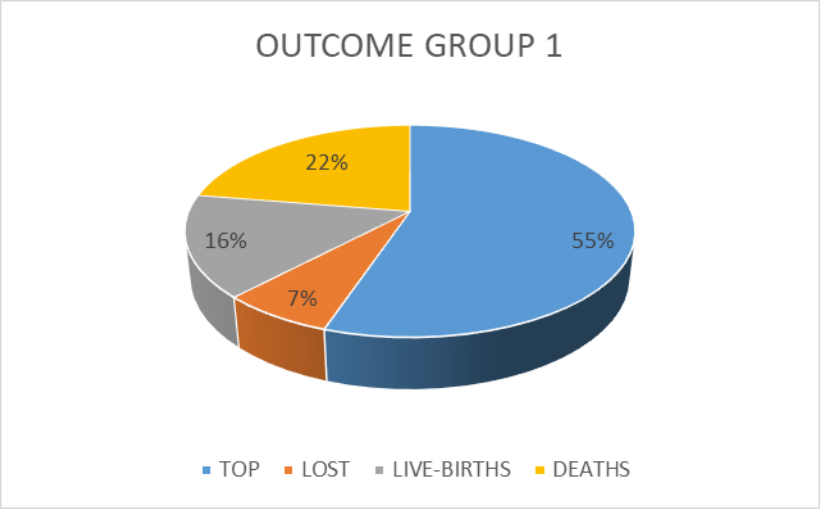
Aortic coarctation (CoA) is the most common duct-dependent heart defect not diagnosed on routine physical examination of the newborn. It is estimated that 60% to 80% of infants with isolated CoA are sent home as "healthy". In our analysis we further investigated all diagnoses of suspected pure CoA syndrome, not in association with other cardiac malformations: of 62 diagnoses of suspected prenatal CoA, only 9 (14.5%) developed signs and symptoms of CoA in the neonatal period and needed surgical treatment. In this regard, it should be emphasized that the diagnosis of suspected fetal CoA is one of the most debated problems currently underway. Many diagnostic difficulties occur at prenatal screening, because of a high rate of false negatives and of operator rely [12].

VI) Analysis Group 1

To understand the impact of prenatal diagnosis on the outcome of complex CHD, we analyzed its survival. In the period from 2016 to 2019 between the two centers, 58 diagnoses of univentricular heart, HLHS and heterotaxy syndrome were done: 24 at the Nesima Hospital and 34 at the MPCC.

Of 58 prenatal diagnoses more than half (32 out of 54, 59.3%) decided for TOP (7.7% of all diagnoses of CHD), 4 women were followed in other centers and 22 (40.7%) were conducted full term (Graph. 9). After birth, more than half (13/22, 59%) of infants died after the first surgical stage for palliation in Fontan. At the time of echocardiography diagnosis in women who conducted full-term pregnancy, GA was between the 13th and 38th week of pregnancy: five (22.7%) had GA > 24 weeks and 17 (77.3%) < 24 weeks. The overall mortality in live births is 60% and increases to 76% considering TOP.

Comparison mortality of group 1 with the others underlined how this cardiac malformation is burdened by the highest mortality and prenatal diagnosis have no benefits in this group.



Graphic 8. Outcome of group 1

Diagnostic accuracy and impact on therapeutic strategies

To evaluate the diagnostic accuracy of the fetal echocardiography, we compared the prenatal diagnosis with postnatal diagnosis or autoptical report in the case of TOP. The postnatal diagnosis was divided into correct diagnosis (78%), similar diagnosis (15.5%), in which the anatomical differences were very close, and incomplete diagnosis (6%).

The greatest diagnostic accuracy was found in group 2, with 96.2% correct diagnosis. In group 1 correct diagnoses were 92.6%, in group 3 were 84.4%, and in group 5 were 81.6%. In group 6, all diagnoses were considered correct as it was possible to verify the diagnosis in real-time. Group 4 showed a lower rate of correct diagnosis (61%) since the suspected CoA syndrome belonging to this group: among 62 suspected cases only 9 patients developed CoA after birth, then we decided to classify all suspected CoA not confirmed at birth as a similar diagnosis. By cumulatively considering the correct and similar diagnosis, the diagnostic accuracy of 94% is achieved.

Table 5. Diagnostic accuracy for each group.

GROUPS	CORRECT DIAGNOSIS N (%)	INCOMPLETE DIAGNOSIS N (%)	SIMILAR DIAGNOSIS N (%)	TOT
1	50 (92.6)	3 (5.5)	1 (1.9)	54
2	25 (96.2)	1 (3.8)	0 (0)	26
3	92 (84.4)	10 (9.1)	7 (6.4)	109
4	97 (61)	9 (5.7)	53 (33.3)	159
5	31 (81.6)	2 (5.2)	5 (13.2)	38
6	28 (100)	0 (0)	0 (0)	28

We also evaluated the impact of the discrepancy between pre and postnatal diagnoses on neonatal outcomes. False-positive diagnoses of isolated CoA were intentionally removed, as they couldn't be considered a discrepancy but only a limitation of echocardiographical predictors of neonatal CoA. If, on the other hand, the suspicion of CoA was associated with other cardiac anomalies diagnosed in the prenatal period, it was included in our analysis.

Forbus et al [13] and Gottliebson et al [14] have indicated that the diagnosis of the aortic arch by fetal echocardiography remains challenging.

Prenatal detection of CoA has been reported to be low and usually, it's suspected in the third trimester of pregnancy when ventricular or vascular disproportion is detected. These parameters alone have an overall low diagnostic accuracy that is even lower during the third trimester, as the fetal heart has a normal physiological right-sided dominance that increases with gestation. Several ultrasound cardiovascular parameters associated with the occurrence of CoA have been proposed to potentially improve the detection rate of prenatal diagnosis for CoA [15]. A recent scoring system proposed by Contro et al. [16] showed a good diagnostic performance for isolated CoA and includes the following parameters: minor cardiovascular defects, transverse aortic arch hypoplasia, disproportion at GA < 32 weeks and aortic arch isthmus z-score < -1.5.

The discrepancies between pre-and postnatal diagnoses were classified into 2 subgroups based on their impact on neonatal care. The first subgroup includes all discordant diagnoses with a greater impact, both positive and negative, on the planning treatment in the prenatal period. This group includes patients for whom the different postnatal diagnosis led to a change in medical care as prostaglandin prescription or the necessity to perform an unexpected percutaneous or surgical intervention during the

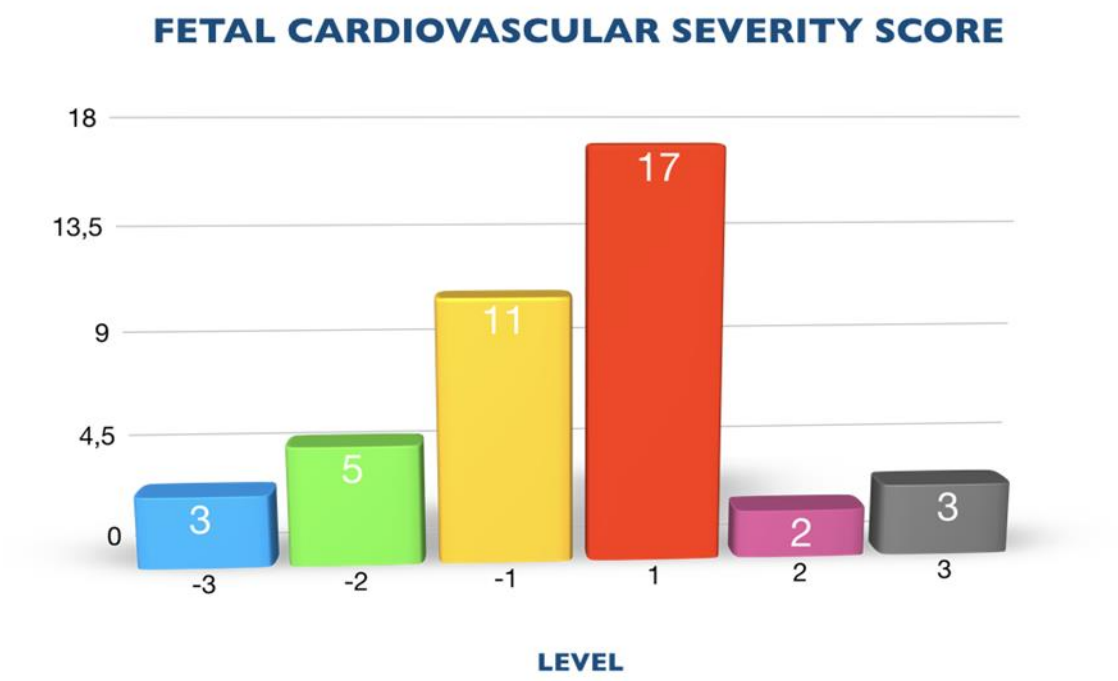
first days of life or, on the contrary, no planning intervention necessary, although planned on an antenatal basis. The second group includes discordant diagnosis without great impact on planned treatment in the prenatal period.

Overall, the discordant diagnosis was 42 of 414 (10%), of these 13 (31%) required a change in the treatment strategy in the neonatal period, specifically one patient required prostaglandins E1 for systemic dependence because of aortic arch interruption was diagnosed at birth; in another case, the Rashkind procedure was not necessary, in 2 patients it didn't need to perform the hybrid procedure (ductal stenting and pulmonary arteries banding) and in the other 9 patients it was necessary to modify the surgery both in the timing than in the technical plan (Table 6).

Table 6. Therapeutic impact of diagnostic discrepancy

DISCORDANT DIAGNOSIS	**N.**	**TOTAL DIAGNOSIS (N. 414) %**	**TOTAL DISCORDANT DIAGNOSIS (N.42) %**
With Impact On Therapy	13	3%	31%
Without Impact On Therapy	29	7%	69%

To assess the global impact of differences between pre-and postnatal diagnosis, we used the Davey-developed fetal cardiovascular disease severity scale [17]. We classified all CHD into 7 severity levels based on the pre-and postnatal diagnosis. We determined that the difference between the severity level between pre-and postnatal was positive if the severity level was lower and negative if it was higher. As shown in table 6, discrepancies between prenatal and postnatal diagnosis changed the level of the severity scale of fatal cardiovascular disease in 42 of 91 cases (10.3% of the total population and 46% of the related-incomplete diagnosis). The severity score was lower in 19 cases (-1 level in 11, -2 levels in 5, and -3 levels in 3). The severity score (Graph. 9) was higher in 22 cases (+1 in 17, +2 in 2 and +3 in 3).



Graph 9. Discrepancy between prenatal and postnatal diagnosis: Severity score.

Discussion

The malformation spectrum of heart disease diagnosed in our fetal population is comparable to that described by other national and international centers (Table 7). The cases of CHD diagnosed at our centers per year are about 17,5 %, close to national and international data [18-21].

According to the literature [18-21], our results show a higher prevalence of prenatal diagnosis of severe CHD and extracardiac and chromosomal associated with CHD than live births diagnosis; this is due to the higher rate of TOP which has a strong impact on this population.

Table 7 shows the most frequent CHD disorders diagnosed in our centres: HLHS (7.3%), VSD (7.3%), AVD (6.8%) and TGA (5.4%).

Table 7. Comparing rate of prenatal diagnosis of CHD.

DIAGNOSIS	Current study %	Fesslova[20] 2015	Chakraborty[19] 2018	Pinheiro[21] 2019	Liu[18] 2019
HLHS	7.5	9.2	13.2	14.5	
UNIVENTRICULAR	4.1	4	3.8	4.2	
TGA	5.4	5.4	9.3	11.5	3.8
CCTGA	0.4	1.5			
TOF	4.5	8	20.9	9.4	4.4
DORV	3.4	6.9	10.4		
TRUNCUS	2	3.4	1.1		
PA + VSD	1.8	2.6		4.2	
VSD	7.3	9.7			35.5
AVD	6.8	12.5	12	7.3	3.5
SA	1.6	2.1		2.1	
COA	16.4	7.5	10.4		3.5
PS/PA	4.3	3.2	1.6		6.2
EBSTEIN	1.8	3.4	0.5	2.1	
CARDIOMYOPHATY	1.8	2.9		2.1	
CARDIAC TUMORS	2.7	1.2			
MISCELLANEOUS	12.8	6.9		9.4	

AS: aortic stenosis, AVD: atrioventricular defect, CCTGA: congenital corrected transposition of great arteries, COA: aortic coarctation, DORV: double outlet right ventricle, HLHS: hypoplasic left heart syndrome, PA: pulmonary atresia, PS: pulmonary stenosis, TGA: transposition of great arteries, TOF: tetralogy of Fallot, VSD: ventricular septal defect.

Defects of the atrioventricular junction and VSD are also the most frequent heart diseases associated with chromosomal and extracardiac anomalies. The presence of CHD in association with chromosomal and extracardiac anomalies affected the decision of TOP in 17 (46%) of 37 cases (8 of group 1, 7 of group 3 and 4 of group 2). Comparing these data with the Italian multicenter study [20], we report a higher rate of TOP associated with chromosomal anomalies, 46% vs 15.7%. The presence of associated extracardiac anomalies (8.5%), as our results show, caused perinatal death in 4 cases (10%) and TOP in 15 cases (40.5%). Our results demonstrate how these anomalies have a statistically significant impact both on the decision of TOP ($p < 0.001$) and on post-natal mortality ($p < 0.012$).

There were no cases of intrauterine death in our patients. The overall TOP was 16.4%, a rate lower than data reported from the Italian multicentre study (21.6%) [20], these data may be partly explained by the lower diffusion of abortion due to different culture in our southern population.

Almost half of TOP (47%) concerns diagnosis of group 1, and in particular, 18 of 68 (26%) were due to HLHS, like the Italian study (26% vs 21%). This group had the highest rate of TOP because of the high mortality that affected this CHD not only in the neonatal period but also in long term.

Large-scale studies [22] have shown a low rate of recurrence of heart defects in affected families, subjected to echocardiographic screening. According to our analysis of 28 (6.3%) pregnant women with a positive family history, 5 (17.8%) were unable to define the familial history, 16 (57%) had malformations different from those presented, 7 (25%) had a recurrence of the same heart disease (2 conotruncal defects and 5 left heart section defects). These data are close to that of other centers in which the exact concordance of recurrent heart disease is shown only in about 21% of cases.

Cumulatively, postnatal mortality was 11.5%, of which 40% (n 15) of all deaths involved group 3, 32% (n 11) group 1, both groups requiring an immediate post-natal surgical or interventional treatment; the remaining 28% concerned the other groups, while no deaths were recorded in arrhythmic patients.

Our data confirm that the only group with the highest mortality ($p < 0.001$) remains group 1 including CHD treatable only with palliative surgery as confirmed in the literature [23].

In all of our series, major rhythm disorders were diagnosed in 11 fetuses: 9 (32.1%) with SVT and 2 (7.1%) with AVB. These data partially overlap with the results of a 10-year observational study, in which fetal tachyarrhythmias were present in 41.4% of cases and bradyarrhythmias in 17.2%. Overall, malignant fetal arrhythmias such as complete AVB and SVT are very rare 29 with an incidence of 1: 5000 pregnancies. Genetic studies have shown a correlation with mutations in the GATA4, NKX2-5, TBX3 and TBX5 genes responsible for the structural and conduction system development of the heart [24]. In our analysis, SVT has the worst prognosis among fetal arrhythmias caused to the high risk of heart failure and hydrops for HR above 180 bpm. Out of 9 recorded cases of tachyarrhythmias, 4 were treated through amiodarone, flecainide, or digitalis to the mother, 2 pregnant women underwent to emergency cesarean section and the other 3 were followed up by close echocardiographic follow-up. From the etiological point of view, no correlation with maternal or family risk factors was found.

The greatest diagnostic accuracy was found in the TGA group 2, (96.2% of correct diagnosis) and group 1 (92.6% of correct diagnosis). By cumulatively considering the correct and similar diagnosis, the diagnostic accuracy of 94% is achieved.

About 10% of all diagnoses showed a discrepancy between the pre and postnatal diagnosis, of which 31% required a change in the treatment strategy of the neonatal period. The discrepancy between pre and the postnatal diagnosis changed the level of fetal cardiovascular disease severity scale in 42 cases (10.3% of the total population and 46% of similar diagnoses). Most of the differences lie within level -1 and +1 (28 out of 42), thus indicating a slight departure from the correct diagnosis, as also reported in data by Bensemlali et al [12].

Limits

In our study, it was not possible to assess the sensitivity and specificity of fetal echocardiography as most of the pregnant women followed in our clinics delivered in other hospitals and then, it was not possible to confirm the prenatal diagnosis, as well as 5% of the pathological diagnosis, were followed in other centers.

Missing data regarding CHD without a prenatal diagnosis prevented the comparison of the outcome of patients with and without a prenatal diagnosis.

Conclusions

The impact of prenatal diagnosis on CHD is crucial in pediatric cardiac practice. In countries where prenatal echocardiographic assessment is standard, a relevant reduction in the prevalence of live births with CHD has already been demonstrated [25]. Prenatal echocardiography has the potential to provide a first-line defense in preventing poor outcomes by ensuring the birth of affected infants into the appropriate level of care [26]. In our analysis, the prenatal diagnosis most influenced the heart diseases in group 1, since these cardiac malformations have high mortality, the prospect offered to parents to be able to choose TOP inevitably leads to a reduction in the prevalence rate of CHD.

In our study, the diagnostic accuracy of fetal echocardiography was high as only in 10% of patients there was a discrepancy between prenatal and postnatal diagnosis, and specifically analyzing the impact that this discrepancy had on the treatment planned at birth, it was seen that the discordant diagnosis differed little from the diagnosis at birth, therefore it did not significantly affect the type of antenatal treatment planned.

Besides, the natural intrauterine evolution of some of these lesions is still being defined, as in the case of aortic stenosis, a disease that, if diagnosed in mid-gestation, can remain invariable or can progress

towards endocardial fibroelastosis. The lack of physiological data makes difficult the work of fetal echocardiography, as misdiagnosis can make the difference between a critically ill infant who needs urgent intervention and a stable infant who will require an election intervention at birth.

Certainly, prenatal diagnosis offers considerable advantages in terms of neonatal survival for all malformations that can benefit from endocrine treatment, the pharmacological treatment for most arrhythmias, and percutaneous treatment in selected cases like aortic stenosis, or intrauterine pacing in complete AVB not responding to cortisone therapy.

The possibility of establishing the treatment necessary at birth is fundamental as it allows to plan delivery in third-level structures equipped with the intensive neonatal unit, cardiology and pediatric cardiac surgery in case of neonatal critical emergency heart diseases, as duct-dependent systemic or pulmonary lesions.

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