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ORIGINAL ARTICLE

Associated Factors with Congenital Heart Disease in the Most Populated State of Brazil Between 2010 and 2018

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Abstract

Background: Cardiac anomalies are the most prevalent congenital malformations among live births in the world. In Brazil, it is estimated that nearly 25,757 new cases occur each year, and the Southeast region presents the highest prevalence, with 10 new cases/1,000 live births.

Objective: The aim of this study is to evaluate the epidemiology of congenital heart disease (CHD) in the state of São Paulo.

Methods: This is a cross-sectional and time-series observational study with data from the Brazilian Information System on Live Births. Heart-related cardiac malformation cases — International Classification of Diseases (ICD) 10th revision Q20.0 to Q24.9 — were selected from January 2010 to December 2018, in the state of São Paulo, Brazil. This study analyzed rates of malformations per year and investigated associated factors, using single and multiple logistic regression models. The significance level adopted in this study was 5%.

Results: The highest cardiac malformation rate was in the São Paulo metropolitan region (2.84:1000), while the lowest was found in the region of Franca (0.3:1000). The most frequent defect was interatrial communication (38.2%). The main associated factors observed in this study were prematurity of 22 to 27 weeks (OR=4,401 95% CI: 3,796-5,104) — CI: Confidence Interval; OR: Odds ratio —, mother's age between 35 and 49 years of age (OR=1,602 95% CI: 1,525-1,682), yellow race (OR=1,481 95% CI: 1,235-1,775), triple or more pregnancy (OR=1,438 95% CI: 1,004-2,060), and history of a dead child (OR=1,213 95% CI: 1,152-1,277).

Conclusion: The main factors associated with this outcome, which are part of the obstetric history of mothers, should be addressed and considered when pregnancy is a planned event.

Keywords: Congenital Heart Disease; Epidemiology; Interatrial Block; Hypoplastic Left Heart Syndrome.

Introduction

Congenital heart diseases (CHDs) are anomalies of the heart that affect its structure and functionality, related to genetic and/or environmental factors. They vary according to their severity, from anomalies that spontaneously improve, to those requiring medical intervention.[1]

Between the third and fourth weeks of gestation, the main elements of the cardiovascular system begin its development and the primitive heart begins to beat. At the end of this period, it is possible to detect the blood flow of the fetus through Doppler ultrasound.[2]

At the end of the fourth week of gestation, the septation of the primitive heart begins, when it takes the form of a heart with four separate chambers, with the development of interventricular and interatrial septa and the heart valves. Thus, it is intuitive to realize how important this period is, since any change in the sequence of development can lead to CHD in the fetus, such as both interatrial and interventricular communications (IVC).[2]

CHDs are the most prevalent congenital malformations among live births in the world[3] and are one of the most fatal diseases in the first year of life.[4] At the end of the first

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decade of the 21st century, a prevalence of 9:1,000 live births with CHD was estimated worldwide.[4] In Brazil, it is estimated that nearly 25,757 new cases occur each year, and the Southeast region presents the highest prevalence, with 10,112 new cases/1,000 live births.[1]

The aim of this study is to evaluate the epidemiology of CHDs in the state of São Paulo, the most populous state in Brazil, from January 2010 to December 2018, identifying associated factors.

Method

This is a mixed-design study. The main study is a cross-sectional, analytical design, investigating the prevalence of a congenital malformation of the heart and their associated factors, while the secondary approach was a descriptive time series study, analyzing the annual prevalence of these during the period of study. Public data was obtained from the Brazilian Information System on Live Births (SINASC, in Portuguese),[5] a part of DATASUS, the official online data source from the Brazilian Ministry of Health**.** The use of public secondary data, without an identification of the participants, dismisses the need for submission to the Ethical Committee.

The cases collected were newborns diagnosed with heart-related cardiac malformations (ICD 10th revision Q20.0 to Q24.9) during the stay at a maternity and reported in the Certificate of Live Births (CLB), from January 2010 to December 2018, in the state of São Paulo.

Data were collected on mother's age, mother's marital status, mother's level of education, pregnancy, prenatal appointments, biological sex, Apgar score at fifth-minute, race/color, and birth weight. The variable number of dead children was categorized as dead child history (yes or no). The continuous variable birth weight was classified into 4 groups: normal weight (≥ 2,500g); low birth weight, between 2,499 and 1,500g; very low birth weight, between 1,499 and 1,000g; and extremely low birth weight (<1,000g). Maternal age was categorized as adolescent (19 years of age and younger), young adult (20 to 34 years of age), adult (35 to 49 years of age), and elderly (50 years of age and older).

The state of São Paulo is divided into 17 Regional Health Departments (RHD), responsible for coordinating and articulating the activities of the State Department of Health. A variable indication of RHD births was created to investigate the pattern of the regional occurrence of malformations.

Statistical Analysis

Descriptive analyses of all study variables were performed. Categorical variables were presented according to their absolute and relative values.

To compare the number of congenital cardiac malformations in RHDs, cardiac malformation rates (CMR) were calculated, where:

$$CMR = \frac{n^{o} \text{ of cardiac malformation in RHD}}{\text{total of newborns in RHD}} \times 10^{3}$$

The analysis of associated factors with cardiac malformation was performed using logistic regression models. The variables were divided into three groups: those related to the mother (mother's level of education, mother's marital status, pregnancy, dead child [abortions and stillbirths],[6] mother's age, pre-natal appointments, and pregnancy), those related to the newborn (biological sex, race/color), and external variables (RHD). For each of these groups, single logistic regression models were defined, including factors that presented biological plausibility, considered to be factors that lead to the outcome. The variables with statistical significance lower than 20% were included in multiple models per group, and those with statistical significance lower than 5% in multiple models were included in the final logistic regression model.

For statistical analysis, the SPSS 14.0 application for Windows was used.

Results

From 2010 to 2018, 5,496,668 births were recorded in the state of São Paulo. Of these, 5,455,437 (99.2%) occurred in health facilities, 64,859 (1.2% of all births) were reported with some type of congenital malformation, with 9,618 cases of CHDs (14.8% of malformations in general). From the total cardiac malformations, 20.5% presented no specific diagnosis. Our study found that, in the state of São Paulo the prevalence was 1.76 per 1,000 live births.

Table 1 presents the descriptive analysis of the variables obtained in the SINASC database. More than three-quarters of all mothers were young adults. However, proportionally, there were more CHDs among the children of adult and old mothers. The percentage distribution of CHD cases was similar among all groups of maternal marital status, as was the distribution between biological sexes. Mothers with a higher level of education presented a higher percentage of children

Table 1 – Descriptive analysis (number and percentage) of the variables used in this study

Variable	Absolute frequency (n = 5.496.668)	Relative frequency (%)	Absolute frequency of cardiac malformation	Relative frequency of cardiac malformation (%)
Mother's age				
Teenager (≤19)	758,139	13.8	1,053	0.14
Adult (35-49)	847,352	15.4	2,489	0.29
Elderly (50 ou +)	660	0.0	2	0.30
Young adult (20-34)	3,890,517	70.8	6,074	0.16
Mother's marital status				
Single	2,333,391	42.5	3,989	0.17
Married	2,253,166	41.0	4,115	0.18
Widow	10,101	0.2	18	0.18
Separated/divorced	95,390	1.7	177	0.19
Consensual union	767,624	14.0	1,280	0.17
Mother's schooling				
None	9,555	0.2	16	0.17
1 to 3 years	75,444	1.4	93	0.12
4 to 7 years	678,620	12.3	978	0.14
8 to 11 years	3,463,682	63.0	5,479	0.16
12 or more	1,237,217	22.5	3,027	0.24
History of dead child				
Yes	839,227	15.3	1,934	0.23
No	4,503,433	81.9	7,654	0.17
Gestation				
<22 Weeks	2,189	0.0	4	0.18
22-27 Weeks	27,586	0.5	189	0.69
28-31 Weeks	53,785	1.0	358	0.67
32-36 Weeks	512,436	9.3	1,745	0.34
37-41 Weeks	4,791,171	87.2	7,194	0.15
≥42 Weeks	83,208	1.5	116	0.14
Pregnancy				
Only	5,362,370	97.6	9,201	0.17
Double	128,308	2.3	383	0.30
Triple or more	3,573	0.1	31	0.87
Appointments				
None	61,206	1.1	92	0.15
1 to 3	205,310	3.7	479	0.23
4 to 6	934,976	17.0	1,687	0.18
7 or more	4,260,108	77.5	7,302	0.17
Biological Sex				

Male	2,815,781	51.2	4,945	0.17
Female	2,680,136	48.8	4,639	0.17
Apgar of the fifth minute				
Severe Asphyxia(0-3)	16,273	0.3	239	1.47
Moderate Asphyxia (4-6)	36,802	0.7	410	1.11
Mild Asphyxia (7)	54,729	1.0	458	0.84
Good Vitallity (8-10)	5,361,825	97.5	8,471	0.16
Race/Color				
White	3,370,328	61.3	5,580	0.16
Black	260,087	4.7	599	0.23
Yellow	29,932	0.5	124	0.41
Brown	1,771,664	32.2	3,280	0.18
Indigenous	8,665	0.2	16	0.18
Weight				
Normal (>2500g)	4,990,346	90.8	7,088	0.14
Low weight (1.500-2.499g)	425,472	7.7	1,857	0.44
Very low weight (1.000-1.499g)	45,558	0.8	407	0.89
Extreme low weight (<1.00g)	34,385	0.6	266	0.77
RHD				
Grande São Paulo	2,749,021	50.0	7,798	0.28
Araçatuba	84,368	1.5	38	0.05
Araraquara	109,942	2.0	59	0.05
Baixada Santista	222,876	4.1	162	0.07
Barretos	47,082	0.9	18	0.04
Bauru	194,582	3.5	115	0.06
Campinas	530,276	9.6	510	0.10
Franca	80,609	1.5	24	0.03
Marília	133,023	2.4	55	0.04
Piracicaba	173,166	3.2	120	0.07
Presidente Prudente	90,171	1.6	54	0.06
Registro	37,824	0.7	12	0.03
Ribeirão Preto	88,067	1.6	56	0.06
São João da Boa Vista	124,830	2.3	112	0.09
São José do Rio Preto	162,203	3.0	114	0.07
Sorocaba	371,127	6.8	220	0.06
Taubaté	289,187	5.3	142	0.05
TOTAL	5,496,668	100	9,618*	100

**Missing data were excluded from the table. RHD: Regional Health Departments.*

with CHD, as did those with a history of having lost at least one child (20%).

It was observed that the more premature the newborn, the higher the percentage of those born with CHD. Regarding the type of pregnancy, a five-fold greater result was observed for cardiac malformations in triple or more pregnancies when compared to single pregnancies. The percentage of CHD among yellow newborns was at least twice as high as other races. The cardiopathic newborn tended to present lower Apgar scores in the fifth minute. The number of prenatal appointments did not influence the occurrence of CHDs, since there was no percentage difference between the appropriate prenatal group and the inadequate prenatal group. In relation to children born with normal weight, the presence of CHD among children with low, very low, and extremely low weight was three to six times higher.

Figure 1 illustrates the annual distribution of congenital malformations and CHDs. Between 2010 and 2018, there was a 2.5-fold increase in the rate of cardiac malformations in the state of São Paulo, while for total congenital malformations it was 1.4-fold higher in the same period.

Table 2 presents a ranking of the 10 most frequent types of CHD in the studied period. There was a higher prevalence of interatrial communication (ASD), followed by unspecified malformation of the heart and IVC. Moreover, 87.5% of the newborns presented non-cyanotic heart diseases. In relation to cyanotic heart diseases, hypoplastic left heart syndrome (HLHS) and tetralogy of Fallot were the most frequent.

It was observed that 1,305 newborns (13.57%) had more than one cardiac malformation, and 1,044 (10.85%) had two associated heart defects, 198 (2.06%) had three, 43 (0.45%) had four, and 20 (0.21%) had five. The most frequent association was IVC with interatrial communication with 268 cases. The second most frequent, with 44 cases, was an association of three CHDs – IVC, ASD, and patent ductus arteriosus.

Table 3 shows the percentage of cardiac malformations with no specific diagnosis (Q24.9) compared to the total number of heart diseases per RHD. The worst situation was observed in Barretos, followed by Franca, Registro, and Araraquara. The best-case scenarios were observed in the São Paulo Metropolitan Region and Baixada Santista.

Table 4 presents the results of multiple logistic regression models. Associated factors included: birth between 22 and 36 weeks of gestation, maternal age between 35 and 49 years, black and yellow races, and history of stillbirth. Triple or more pregnancy was a factor directly associated with the outcome, as compared to a single pregnancy. In relation to maternal education, having one to 11 years of schooling was a factor associated with the absence of cardiac malformation, when compared to 12 years or more. Compared to the São Paulo Metropolitan Region, no RHDs were associated with congenital cardiac anomalies. The other variables tested showed no significant relationship with the outcome.

Discussion

In the analyzed period, the main CHDs were, in order of frequency: ASD, unspecified malformation of the heart, IVC, and HLHS.

Regarding the factors associated with the malformation, our study found prematurity, maternal age between 35 and 49 years, yellow and black races, triple or more pregnancy, and obstetric history of a stillbirth.

This study was population-based and analyzed a long period of data in São Paulo. This state is the most populous and developed state of Brazil. It has the highest gross domestic product (GDP) compared to the other states of the country, according to Ministry of Economic Development.[7] Furthermore, the Human Development Index (HDI) of this state is considered high, at 0.783.[7] The HDI takes into consideration three main elements of human development: longevity, education, and population income.[7] The coverage of the health system is extensive, and this can be observed from the number of births that occurred in health facilities.[8] The possibility of error in the diagnosis of CHDs at birth exists; however, compared with other states of the country, it tends to be lower, given the existing infrastructure.[8]

SINASC is a national birth data collection system, adopted in all municipalities of the country and records events that occurred in both the public and private subsystems. Implemented gradually since the 1990s, the quality of data in CLB forms has consistently improved in recent decades.[9] Thus, it can be considered the main and most relevant database on live births for population-based research in Brazil.

Despite the improved coverage and quality of the data, this is a secondary database with characteristic limitations. The lack of echocardiogram during the prenatal follow up, a limited number of specialized centers, underreporting, and the length of stay of the newborn in the hospital are factors that may underestimate the results, since some diseases do not present hemodynamic severity, as they

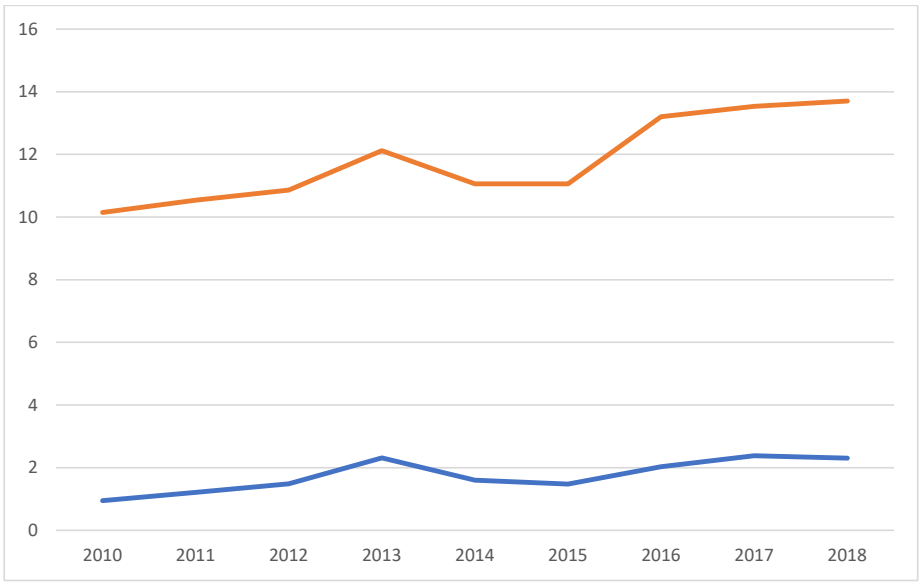

Figure 1 – Rate of total congenital malformations and malformations of the heart in São Paulo state from 2010 to 2018.

Table 2 – Frequence of CHD diagnosed in perinatal period of life in São Paulo state from 2010 to 2018

Classification	Type of Malformation of the Heart	ICD10	Total
1º	ASD	Q21.1	3677
2º	Unspecified malformation of the heart	Q24.9	1971
3º	IVC	Q21.0	1595
4º	HLHS	Q23.4	433
5º	Tetralogy of Fallot	Q21.3	427
6º	Other Specified Congenital Heart Malformations	Q24.8	336
7º	Atrioventricular communication	Q21.2	261
8º	Isomerism of atrial appendages	Q20.6	214
9º	Ventriculoarterial discordance	Q20.3	211
10º	Other congenital malformations of chambers and cardiac communications	Q20.8	202

ASD: interatrial communication; IVC: interventricular communication; CHD: congenital heart disease; HLHS: hypoplastic left heart syndrome.

are not identified within the first hours of life.[1,10-12] This is directly associated to the results found in the present study, since the second most frequent diagnosis was unspecified malformations of the heart.

The prevalence of CHD worldwide ranges from 8:1000[1,3] to 9:1000[1] live births. Regarding the prevalence on the American continent, in the USA, this estimate was 2 to 3 per 1,000 live births in 2015,[13] while in Colombia it was 1.2 per 1,000 live births in 2006.[14] In the state of São Paulo, it was observed that the prevalence was 5.7-fold lower than that estimated for the country. Thus, it is possible to affirm that the prevalence of these diseases around the world are most likely related to access to the diagnoses and

Table 3 – Rate of unspecified congenital malformation of the heart according to regional health divisions in São Paulo state

Regional health divisions	Rate of unespecified malformation of the heart	Rate of especified congenital malformation of the heart
1 - Grande São Paulo	0,167478841	2,83664621
2 - Araçatuba	0,289473684	0,450407738
3 - Araraquara	0,457627119	0,536646595
4 - Baixada Santista	0,179012346	0,726861573
5 - Barretos	0,611111111	0,382311711
6 - Bauru	0,330434783	0,591010474
7 - Campinas	0,403921569	0,961763308
8 - Franca	0,5	0,297733504
9 - Marília	0,363636364	0,413462334
10 - Piracicaba	0,375	0,692976681
11 - Presidente Prudente	0,277777778	0,598862162
12 - Registro	0,5	0,317258883
13 - Ribeirão Preto	0,375	0,635879501
14 - São João da Boa Vista	0,419642857	0,897220219
15 - São José do Rio Preto	0,324561404	0,702823006
16 - Sorocaba	0,368181818	0,592788991
17 - Taubaté	0,408450704	0,491031755

notifications of these diseases, which can be attributed to the socioeconomic and infrastructure conditions of the health system of each country.

Epidemiological studies with different designs[1,15] have shown ventricular septal malformations as the most frequent CHD in Brazil. Our study observed that, in the state of São Paulo, the main defect reported was ASD. Many cardiac malformations were not specified, but even if all of these were defects of interventricular septal defects, they would still be less frequent than atrial septal malformations.

Lara and Solis[16] showed ASD, IVC, and HLHS as the most frequent malformations diagnosed in newborns. In our study, HLHS was the fourth more frequent cause. It is important to mention that this condition is one of the critical CHDs, which commonly appear in the perinatal period, given its hemodynamic severity.[17] Thus, other congenital cardiopathies may have been under-diagnosed during the same period, considering the low severity.

According to our study, non-cyanotic heart diseases were seven times more frequent than cyanotic diseases, which is similar to the findings of Rohit et al.[11] in Nigeria; Cappellesso and collaborators[18] in Manaus, Brazil; and Abqari et al.[12] in India.

Petrossian and collaborators[19] showed a relation between some cardiac malformations, mainly conotruncal heart defects, atrial septal defect, and birth weight deficits. It is not clear whether these weight deficits can be considered low birth weight or simply small for the gestational age. In our study, a low birth weight variable and a fifth minute Apgar score were not included in the logistic regression model due to the uncertainty of biological plausibility to be associated with cardiac malformation.

Prematurity was directly related to the outcome, which agrees with the study of Rocha et al.[20] It should be highlighted that the formation of the heart is complete around the eighth week of gestation[2] and that premature delivery alone is not directly related to most of the malformations. It is likely that the presence of CHD may function as a determining factor of preterm delivery, as shown by Laas and collaborators.[21]

Table 4 – Multiple logistic regression for congenital heat desase and explanatory variables

Explanatory variables		OR (CI 95%)
Gestation	37-41 weeks	1.00
	< 22 weeks	0.728 (0.182-2.914)
	22-27 weeks	4.401 (3.796-5.104)
	28-31 weeks	4.325 (3.875-4.828)
	32-36 weeks	2.257 (2.137-2.383)
	≥ 42 weeks	1.100 (0.913-1.325)
Mother's age	Teenager (≤19)	0.974 (0.909-1.043)
	Adult (35-49)	1.602 (1.525-1.682)
	Elderly (≥50)	1.436 (0.357-5.778)
	Young adult (20-34)	1.00
Race/color	White	1.00
	Black	1.195 (1.096-1.302)
	Yellow	1.481 (1.235-1.775)
	Brown	0.997 (0.952-1.044)
	Indigenous	0.913 (0.558-1.494)
Pregnancy	Only	1.00
	Double	0.911 (0.818-1.014)
	Triple or more	1.438 (1.004-2.060)
History of dead child	No	1.00
	Yes	1.213 (1.152-1.277)
Mother's schooling	None	0.716 (0.437-1.172)
	1 to 3 years	0.598 (0.486-0.737)
	4 to 7 years	0.689 (0.637-0.744)
	8 to 11 years	0.743 (0.707-0.780)
	12 or more	1.00
Mother's marital status	Single	1.00
	Married	0.967 (0.922-1.015)
	Widow	0.870 (0.539-1.402)
	Separated/divorced	0.942 (0.808-1.099)
	Consensual union	0.954 (0.895-1.017)
RHD	1 – Grande SP	1.00
	2 – Araçatuba	0.194 (0.141-0.268)
	3 – Araraquara	0.196 (0.151-0.254)
	4 – Baixada Santista	0.269 (0.230-0.315)
	5 – Barretos	0.143 (0.090-0.227)
	6 – Bauru	0.226 (0.188-0.273)
	7 – Campinas	0.339 (0.309-0.372)
	8 – Franca	0.106 (0.069-0.162)
	9 – Marília	0.155 (0.119-0.203)
	10 – Piracicaba	0.250 (0.208-0.300)
	11 – Presidente Prudente	0.226 (0.173-0.296)
	12 – Registro	0.122 (0.067-0.220)
	13 – Ribeirão Preto	0.243 (0.187-0.318)
	14 – São João da Boa Vista	0.315 (0.260-0.382)
	15 – São José do Rio Preto	0.258 (0.214-0.311)
	16 – Sorocaba	0.218 (0.190-0.250)
	17 – Taubaté	0.231 (0.194-0.275)
Biological Sex	Male	1.002 (0.963-1.043)
	Female	1.00

CI: Confidence interval; RHD: Regional Health Departments.

Regarding advanced maternal age (34-49 years of age) as a factor associated with CHDs, other studies[16,17,12,20,22] give support to our results. This can be attributed to the greater tendency of genetic alterations with consequent chromosomal syndromes in children of this mother's age group, which are usually associated with a higher incidence of CHDs, as occurs in the trisomy 21 chromosome, for example.[11]

In relation to multiple gestations, it was seen in our study that cardiac malformations were more frequent in triplets. Triple or more pregnancies use to be frequent in both *in vitro* fertilizations (IVF) or intracytoplasmic sperm injection (ICSI), and there is an association with these types of artificial conception and CHDs.[23] In our study, this investigation was not possible, since this type of information is not included in the database.

Regarding the race/color variable, a significant association was found with the outcome in the yellow and black races. One study conducted in Taiwan[24] also presented a high prevalence in this region's population, as well as throughout Asia[3], when compared with other continents, which can be related to the predominance of CHD in the yellow race. However, Cappellesso et al.,[18] in

a study conducted in Manaus, found a predominance in the brown race. It is possible that this association could be explained by the exposure to teratogenic agents, according to race, culture, socioeconomic status, and religion. However, the use of secondary data limits this kind of assumption.

Our study found an association between triple pregnancies, or with more fetuses, and the presence of cardiac malformations. The specialized literature does not address this condition as a determinant for the occurrence of anomalies, and further studies need to be conducted in order to better explore this potentially associated factor.

The analysis by RHDs was done in an attempt to identify some pattern of spatial distribution of the outcome in the state of São Paulo. When compared to the Greater São Paulo metropolitan area, an area that includes the state capital, the other RHDs were not a factor associated with the occurrence of malformations. In this respect, the presence of greater technological resources in RHD-I can make this area the site with the highest early diagnosis of CHDs.

Pinto et al.[25] found nearly 50% of mothers of children with CHD had a history of stillbirth, a result that is two and a half times higher than that found in the present study. However, when multiple logistic regression was performed, this characteristic was a factor strongly associated with CHD (Table 3), which agrees with the study by Abqari et al.[12], who also obtained a result similar to that found in this study.

No significant association was found between biological sex and cardiac malformation in the state of São Paulo. There is much disagreement in the literature regarding the proportional distribution of frequencies in this variable. One study[26] found a higher prevalence in females, two other studies[18] found it in males, while another two studies[11,27] found a result similar to ours.

Women with a higher level of education tend to become pregnant later, possibly due to entry into the labor market. Thus, becoming pregnant at an advanced age could contribute to the higher probability of genetic mutations in the fetus.[12, 22] Lower education is associated with lower income, exposure to infections, and malnutrition, which may contribute to an increase in cardiac malformation.[28] However, our study found no association of this variable with the outcome in the logistic regression model, contrary to the hypothesis presented above.

Currently, there is a greater interest in studying the genetic determination of malformations in the literature, with less concern about the epidemiological profile.[29,30] In this context, the present study is relevant, when formulating the epidemiological analysis of cardiac malformations in the state of São Paulo.

Conclusion

It can be concluded that the occurrence of CHDs with an early diagnosis in the State of São Paulo presented a pattern of occurrence similar to that observed in other places, and some of the factors associated with this outcome, which are part of the obstetric history of mothers, should be addressed and considered whenever pregnancy may be a planned event. The adequacy of the health service can help predict the presence of malformation and provide adequate follow-up of pregnant women and their concepts.

Author contributions

Conception and design of the research, acquisition of data, analysis and interpretation of the data, statistical analysis, writing of the manuscript and critical revision of the manuscript for intellectual content: Madriga I, Baldini C, Prado C, Dunder T, Braga ALF.

Potential Conflict of Interest

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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