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Risk factors characterisation for CHD: a case–control study in Bogota and Cali, Colombia, 2002–2020

Esteban Portilla R.[1], Vyara Harizanov[1], Karen Sarmiento[2], Jorge Holguín[3], Gloria Gracia[4], Paula Hurtado-Villa[5] and Ignacio Zarante[6]

[1]Faculty of Medicine, Pontificia Universidad Javeriana, Bogotá, Colombia; [2]Department of Physiological Sciences, Faculty of Medicine, Pontificia Universidad Javeriana, Bogotá, Colombia; [3]Secretary of Public Health, Cali, Colombia; [4]Secretary of Health, Bogotá, Colombia; [5]Department of Basic Sciences, Faculty of Health, Pontificia Universidad Javeriana, Cali, Colombia and [6]Institute of Human Genetics, Faculty of Medicine, Pontificia Universidad Javeriana, Bogotá, Colombia

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Corresponding author: Esteban Portilla R.;
Email: eportilla@javeriana.edu.co

Abstract

Objective: CHDs correspond to 28% of all congenital anomalies, being the leading cause of infant mortality in the first year of life. Thus, it is essential to explore risk factors for CHDs presentation, allowing the detection of probable cases within a population. *Methods:* We identified newborns with CHDs within a cohort from the Program for the Prevention and Monitoring of Congenital Defects in Bogota and Cali, 2002–2020. Cases were classified as isolated, complex isolated, polymalformed, and syndromic. Variables were analysed by comparing case and control averages with Student's t test using a 95% confidence level. *Results:* Prevalence obtained was 19.36 per 10 000 live births; non-specified CHD, ventricular septal defect, and atrial septal defect were the most prevalent. As risk factors were found: paternal and maternal age above 45 years, pregestational diabetes, mother's body mass index above 25, low educational level, and socio-economic status. As protective factors: folic acid consumption within the first trimester and pregestational period. *Conclusion:* Different risk and protective factors associated with the presentation of CHDs have been described. We consider that public health strategies should be aimed to reduce risk factors exposure. Also, improving diagnosis and prognosis by having a close monitoring on high-risk patients.

CHD are described as structural or functional defects that occur in the heart or great vessels,[1] corresponding to 28% of all congenital anomalies[2] with a prevalence between 40 and 100 cases per 10 000 live births.[3] The Latin American Network for Congenital Malformations (ReLAMC) reported a prevalence in 2019 of CHD for Latin America of 15.53 cases/10 000 LB (95% CI 15.27–15.79).[4] According to the Colombian National Institute of Health (INS),[5] CHD represent 20.5% of all congenital anomalies in Colombia, with a prevalence in Bogota of 59.76/10 000 LB (95% CI 51.24–68.27) and in Cali of 11.55 (95% CI 8.01–15.08) (4).[4]

Worldwide, CHD are the leading cause of infant mortality during the first year of life.[6] In Colombia, between 1992 and 2008, infant mortality secondary to CHD was 32% including fetal and neonatal deaths,[7] being 2.7% in Bogota and Cali for 2001–2014.[8] Nowadays, the most frequent CHD are patent ductus arteriosus, ventricular septal defect, and atrial septal defect, representing 57.9% of all CHD (1). Nevertheless, according to the European Concerted Action on Congenital Anomalies and Twins (EUROCAT) report, between 2012 and 2017 there has been an increasing trend regarding the prevalence of hypoplastic left heart syndrome of 8.1% and for coarctation of the aorta of 1.8%.[9] In the Program for the Prevention and Follow-up of Congenital Defects and Orphan Diseases of Bogotá and Cali (PREVErDEc by its acronym in Spanish); ventricular septal defect, atrial septal defect, and hypoplastic left heart syndrome were found as the most frequent CHD.[8]

Recent studies have shown different risk factors for CHD presentation; the most relevant are the use of drugs, exposure to toxins or organic solvents,[10] maternal age between 35 and 60 years, and body mass index > 30 kg/m^2,[11] some maternal pathologies such as pregestational diabetes, febrile symptoms, phenylketonuria, and viral infections like influenza.[10,12] Our objective was to perform an epidemiological and risk factors characterisation associated with the presentation of CHD in Bogotá and Cali in the period of 2002–2020 using PREVErDEc data.

Materials and methods

The information included was obtained from administrative surveillance data regarding PREVErDEc, which is linked to the Pontificia Universidad Javeriana, Colombia, Health Secretaries of Bogotá and Cali, the Latin American Network for Congenital Malformations

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Table 1. Case distribution of CHDs

Case groups	Male	Female	Indeterminate	Missing data	Rate per 10 0000 (95% confidence interval)
Isolated	273	244	0	4	9.33 (8.55–10.17)
Complex Isolated	151	89	0	2	4.36 (3.81–4.92)
Polymalformed	134	108	1	2	4.39 (3.86–4.97)
Syndromic	39	33	0	1	1.31 (1.02–1.64)
Total	597	474	1	9	19.36 (18.23–20.55)

(ReLAMC) and the International Clearinghouse for Birth Defects Surveillance and Research. This information was collected within the programme's hospitals through doctors, using medical records at the time of birth, and further information was obtained with maternal interviews. Doctors were previously trained to perform physical examination searching specifically congenital anomalies in the newborn; furthermore after they searched the controls and filled out the forms according to the methodology of Latin American Collaborative Study of Congenital Malformations (ECLAMC).[13]

A retrospective case–control study was carried out, using the methodology of the ECLAMC.[13] Cases were defined as live births or stillbirths weighing 500 g or more with CHD and born in the programme's hospitals between January 2002 and March 2020. Controls were live births without congenital anomalies from the same hospital as the cases, maintaining a 1:4 cases-to-controls ratio.

The prevalence of CHD was established according to the following classification: isolated defined as a case with a single CHD; complex isolated understood as a case with two or more CHD; polymalformed with CHD associated with a major malformation, and syndromic defined as a case of multiple congenital malformations with a recognisable pattern and genetic aetiology (ie, Edwards syndrome).

For the social characteristics, the association with the socioeconomic status was analysed according to the National Administrative Department of Statistics, which classifies individuals on the report of variables like housing characteristics and findings within its community (access to public services and transport). We compare groups 1 and 2 (low) against 3–6 (medium-high). Additionally, maternal education was classified as low educational level (incomplete secondary) or medium-high educational level (completed secondary and/or more studies).

Quantitative variables such as birth height and weight, number of pregnancies, and maternal and gestational age were analysed by comparing case and control averages with Student *t* test using a 95% confidence level. By means of the frequency distribution, the odds ratio with a 95% confidence level was calculated for the variables: maternal, father's and gestational age, patient sex, maternal BMI, presence of gestational or pre-pregnancy diabetes, and folic acid consumption according to the pregestational period and the first trimester. Data were analysed using Microsoft Excel Office 365 and EpiCalc. The statistical analysis for the prevalence of CHD per 10 000 LB was calculated according to the Poisson distribution, with a 95% confidence interval.

Results

A total of 558 255 births were found between 2002 and 2020, 1 081 cases were CHD, which stand by the following distribution: 48.20% (n = 521) isolated cases, 22.39% (n = 242) complex isolated, 22.66% (n = 245) polymalformed, and 6.75% (n = 73) syndromic (Table 1). We found CHD prevalence of 19.36 per 10 000 LB per year (95% CI 18.23–20.55).

Table 2. Distribution of CHDs within isolated cases

Congenital heart disease	Frequency (n)	Percentage (%)
Non-specified CHD	161	30.90
Ventricular septal defect	92	17.66
Atrial SEPTAL DEFECT	63	12.09
Hypoplastic left heart	30	5.76
Aortic coarctation	26	4.99
Patent ductus arteriosus	26	4.99
Other CHD	20	3.84
Transposition of great arteries	18	3.45
Pulmonary valve anomaly	16	3.07
Tetralogy of fallot	15	2.88
Single ventricle	13	2.50
Tricuspid valve anomaly	10	1.92
Dextrocardia	10	1.92
Aortic valve anomaly	9	1.73
Anomalous venous return	6	1.15
Septal defect	4	0.77
Other arterial anomaly	2	0.38
Total	521	100.00

CHD = congenital heart disease.

Regarding isolated cases, the most frequent CHD were non-specified CHD 30.90% (n = 161), ventricular septal defect 17.66% (n = 92), atrial septal defect 12.09% (n = 63), and hypoplastic left heart syndrome 5.76% (n = 30) (Table 2).

The distribution of the patients was 89.5% (n = 968) LB, 8.1% (n = 87) died during hospitalisation; 43.7% (n = 38) female and 56.3% (n = 49) male. Finally, the remaining 2.4% (n = 26) were stillbirths, distributed among 14 females, 10 males, and 2 indeterminates regarding infant sex.

Significant differences were found in birth weight and size means between cases and controls. Additionally, gestational, maternal, and paternal ages also show significant differences (Table 3).

It was found that a maternal age ≥ 36 years is associated with risk of developing CDH. This is enhanced when maternal age is greater than 45 years (OR: 5.05; 95% CI 1.54–16.58), even with no chromosomal anomaly associated (OR: 4.06; 95% CI 1.17–14.07). Similar findings regarding paternal age over 45 years (OR: 1.64; 95% CI 1.12–2.38), alongside a gestational age ≤ 34 weeks (OR: 2.88; 95% CI 2.55–3.24). While the sex of the newborn did not show an association for the development of CHD (OR: 0.99; 95% CI 0.87–1.14) (Table 4).

Additionally, pregestational diabetes is related to CHD occurrence (OR: 7.00; 95% CI 3.20–15.34). Maternal BMI ≥ 25 Kg/m^2 also showed an association (OR: 1.24; 95% CI 1.03–1.48). Regarding social variables, the low educational level of the mother was linked with CHD presentation (OR: 1.22; 95% CI 1.01–1.48), similar results were found for SS ≤ 2 (OR: 1.27; 95% CI 1.04–1.55) (Table 4).

On the other hand, folic acid (FA) supplementation was demonstrated to decrease the probability of presenting CHD in the

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Table 3. Quantitative variable comparison between cases and controls

Variable	Cases (n = 1 081)		Controls (n = 4 394)		p value
	Mean	Standard deviation	Mean	Standard deviation	
Birth weight (g)	2 684.20	736.36	3 018.34	488.91	< 0.01
Birth size (cm)	47.51	4.45	49.51	2.68	< 0.01
Pregnancies	1.70	1.16	1.93	1.09	< 0.01
Gestational age (weeks)	36.83	3.16	38.28	1.83	< 0.01
Maternal age (years)	27.39	7.11	26.70	6.51	< 0.05
Paternal age (years)	30.66	7.86	29.79	7.61	< 0.01

Table 4. Risk factors associated with CHDs

Factors	Cases	Controls	Odds ratio (95% Confidence interval)
Maternal age			
> 45 years	6	5	5.05 (1.54–16.58)
> 45 years without CA†	5	5	4.06 (1.17–14.07)
Paternal age			
> 45 years	36	138	1.64 (1.12–2.38)
Gestational age			
≤ 34 weeks	177	177	2.88 (2.55–3.24)
35-39 weeks	774	3189	0.49 (0.40–0.60)
> 39 weeks	128	956	
Newborn sex (Male)	497	2433	0.99 (0.87–1.14)
BMI (kg/m^2)			
< 18	16	118	0.71 (0.42–1.21)
18-24.9	310	1734	1.24 (1.03–1.48)
≥ 25	135	594	
Diabetes			
Pregestational	17	10	7.00 (3.20–15.34)
Gestational	28	136	0.83 (0.55–1.26)
Folic acid consumption			
Pregestational	2	41	0.20 (0.05–0.81)
1st trimester	360	2357	0.43 (0,38–0,50)
Low educational level (incomplete secondary)	161	823	1.22 (1.01–1.48)
Socio-economic status ≤ 2	294	184	1.27 (1.04–1.55)

†CA = Chromosomal anomaly.

pregestational period (OR: 0.20; 95% CI 0.05–0.81) and in the first trimester (OR: 0.43; 95% CI 0.38–0.50) (Table 4).

Discussion

This study focused on the epidemiological description of CHD and the analysis of risk factors associated with the presentation of this congenital anomaly in 44 hospitals in Bogotá and Cali between 2002 and 2020.

The prevalence of CHD in this study was 19.36 per 10 000 LB (95% CI 18.23–20.55). This is considerably lower than other European countries reported in the EUROCAT, such as Spain, which had a prevalence of 79.37 per 10 000 live births between 2008 and 2017.[9] Such variation could be due to the under-reporting and diagnosis of CHD cases in developing countries like Colombia (8). Although the prevalence was higher than some Latin American countries such as Chile, whose prevalence was 14.76 per 10 000 during the period 2017–2019.[4]

According to Tassinari et al, during the period 2001–2014, in Bogotá the prevalence of CHD was 15.1 per 10 000 LB (95% CI 13.94–16.36),[8] and 11.55 (95% CI 11.01–15.08) in Cali,[4] less than what was found in our study between 2015 and 2020; being 35.94 per 10 000 LB (95% CI 32.68–39.44). We found an increasing trend over the years regarding CHD prevalence, which is presumably due to the implementation of a vigilance programme as PREVERDEC.[8] However, the most frequent isolated CHD was non-specified, revealing the need to improve the prenatal and postnatal diagnostic mechanisms, optimising the specificity in the notification of this malformation.[14]

Regarding birth size and weight, we found significant differences between cases and controls ($p < 0.01$) (Table 3). In spite of that result, these variables are not attributable as CHD risk factors, as they are evident after birth.

Several studies have shown that maternal age > 35 years is a risk factor for CHD,[11,15,16] this result was also found by us, especially for those aged > 45 years, excluding cases with Down syndrome (OR: 5.05; 95% CI 1.54–16.58). However, the findings differ to some extent in comparison to studies carried out in Europe, where this association was not statistically significant.[17–19] We found that 82.4% (n = 28) of syndromic cases in mothers ≥ 36 years old correspond to Down syndrome, suggesting the relationship between these two variables.[20] The impact of this result on public health is high in spite of increasing the probability of CHD presentation, because in 2017 in Colombia, 10.9% (n = 71 712) of births were mothers over 35 years of age.[21]

A previous cohort study by Joinau-Zoulovits et al. showed that paternal age greater than 35 years increases the risk of developing CHD by 16%;[22] while our study found that this risk occurs from an age > 45 years (OR: 1.64; 95% CI 1.12–2.38). This meta-analysis only considers paternal age without maternal age association for CHD presentation. We found that 58.3% (n = 21) of paternal > 45 years have a partner > 35 years, which increases the risk of presenting CHD as previously found; however, other explanations could be considered.

We found that gestational age ≤ 34 weeks was associated with increasing the risk for CHD (OR: 2,88; 95% CI 2.55–3.24). Similar results were obtained by Steurer et al for ≤ 38 weeks[23] and by Chu et al for ≤ 30 weeks.[24] This could be attributable to instances of patent ductus arteriosus, which may arise as a result of prematurity. Even so, low gestational age cannot be addressed as a risk factor for CHD since it is evident after cardiac organogenesis, even though gestational time is an important factor in development.[15,25] Still, it is recommended that each premature newborn have an ideal surveillance and evaluation of possible congenital anomalies.

Additionally, we did not find any association between the sex of the newborn and the risk of developing CHD (OR: 0.99; 95% CI 0.87–1.14). However, there is heterogeneity in terms of the results

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obtained in other studies, since the sex of the newborn was a risk factor, whether it is male,[15] woman,[11] or both.[18] Although the results vary, it is important to note that differences are reported in terms of prognosis and mortality in patients with CHD according to sex, being higher for females.[26] Regarding maternal BMI, different studies have reported an increased risk of presenting CHD for BMI < 18Kg/m^2,[27] when being overweight or obese,[11,15,28] similar to our results when the BMI ≥ 25Kg/m^2 (OR: 1.24; 95% CI 1.03–1.48). Yet, Dolk et al[19] found no association for maternal BMI.

In this study, it is important to recall the association found between pre-pregnancy diabetes and the risk of presenting CHD (OR: 7.00; 95% CI 3.20–15.34), as demonstrated in different studies.[10,18,19,29] Risk association for transposition of great arteries, septal defects and outflow tract defects was also observed.[10] A possible mechanism that explains the relationship between diabetes and the presentation of CHD was proposed by Engineer et al. Where pregestational diabetic patients develop oxidative stress induced by hyperglycaemia, increasing reactive oxygen species and free radicals, allowing cell damage and alteration in gene expression during cardiac morphogenesis.[30] Some works try to reduce the risk through exercise, although it has not been shown as a protective factor in humans.[19] On the other hand, in the same study by Dolk et al[19] gestational diabetes was not a risk factor for CHD, according to our findings (OR: 0.83 95% CI 0.55–1.26); however, it was considered a risk factor for other authors.[12,29]

Different studies demonstrate that FA consumption in the pre-pregnancy period and during any trimester of pregnancy.[10,31] Though our findings highlight the importance of pre-pregnancy FA consumption for the prevention of CHD (OR: 0.20; 95% CI 0.05–0.81) and during the first trimester of pregnancy (OR: 0.43; 95% CI 0.38–0.50) allowing optimal levels of FA prior to the period of cardiac morphogenesis. In addition, this finding is supported by the risk of presenting CHD that is reported by the use of FA antagonists (OR: 7.7; 95% CI 2.8–21.7).[32] In Colombia, the resolution 3280 of 2018 of the Ministry of Health and Social Protection establishes the supplementation of FA and micronutrients 0.4mg/day in the gestational period, and for those mothers with history of births with congenital defects, a dose of 4mg/day has to be initiated 3 months before pregnancy.[33]

It is important to recognise the role of FA in the context of cardiac development, in that it is required for cell maintenance and division, as well as for the construction and repair of DNA.[34] Therefore, a daily intake of 400 μg is recommended through diet or using supplements.[34] In Colombia for 2011, 89 unintended pregnancies were estimated per 1 000 women of reproductive age,[35] so there is a public health problem regarding late multivitamin supplementation. Thus, the fortification of rice with FA is an important prevention strategy, for 2017 it was calculated that 35% of the rice was fortified.[36]

The meta-analysis carried out by Yu et al showed that the low SS (OR: 1.05; 95% CI 1.01–1.09) and the mother's low educational level (OR: 1.11; 95% CI 1.03–1.21) are risk factors for the presentation of CHD,[37] which agrees with our findings for low SS (OR: 1.27; 95% CI 1.04–1.55) and mother's low educational level (OR: 1.22; 95% CI 1.01–1.48), respectively, similar findings in other study.[38] On the contrary, Dolk et al did not find a significant association for any SS, but the mother's low educational level was associated with CHD (OR: 1.63; 95% CI 1.13–2.34).[19]

In developing countries, low SS is a risk factor for CHD since it represents having less access to health services and education about contraceptive mechanisms and the preconception and prenatal care that must be taken.[39] Additionally other factors are linked to early age pregnancies and thus with risk behaviours such as folic acid deficiency. Likewise, maternal malnutrition and exposure to teratogenic agents is reflected in low SS due to the scarcity of resources to live in optimal environments,[40] factors that are possibly associated with the appearance of CHD, still other explanations can be considered.

In Colombia, a mandatory maternal-perinatal health care route is established for all pregnant women and its costs are covered by the health system. It includes two prenatal ultrasounds, one between weeks 11 and 14 to evaluate aneuploidies, and another between weeks 18 and 24 to evaluate structural abnormalities. Factors such as late diagnosis of pregnancy, the socio-economic conditions of patients, and the lack of adherence to prenatal programmes influence the fact that this route is not fulfilled for some pregnant women. As we have previously described, prenatal detection of CHD is around 30% in Bogotá and Cali, and this also tends to increase under-reporting.[41]

The study's main limitations are incomplete records within the surveillance and monitoring system, affecting the sample space for the different analyzes, as well as the memory bias that occurs in mothers on behalf it is a retrospective study.

Conclusion

This study analysed the different risk and protective factors associated with the presentation of CHD. We found maternal and paternal age > 45 years, in addition to pregestational diabetes, maternal BMI ≥ 25 kg/m^2, low SS, and educational level as risk factors for CDH development. We also found that folic acid intake in the pregestational period and during the first trimester of pregnancy are protective factors for the same outcome. This highlights the importance of primary prevention measures for CHD and the implementation of diagnostic and notification methods for congenital anomalies, improving the outcome of mortality and prognosis.

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