CARDIOLOGÍA PEDIÁTRICA - ARTÍCULO ORIGINAL

Risk factors for congenital heart disease: A case-control study

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Abstract
Objective: to investigate the prevalence and risk factors in newborns with congenital heart defects (CHD).
Methods: this case-control study included 234,386 births from January 2006 to June 2013 that were evaluated and registered in the Latin-American Collaborative Study of Congenital Malformations (ECLAMC) methodology, establishing the Bogota Birth Defects Surveillance and Follow-up Program (BBDSFP).
Results: 234,368 births were registered and 277 of them were identified to have a CHD. The most common defect among all was ventricular septal defect (13.7%) followed by atrial septal defect (10.1%). As main associations we obtained: having any type of pre-gestational diabetes mellitus had an increased risk for the development of CHD (OR 16.36 CI: 4.54–58.35). Low weight newborns (less than 2,500 g) (OR: 4.13 CI: 3.13–5.44) and a gestational age lower than 36 weeks (OR: 4.92 CI: 3–5.44) were also linked to malformations.
Conclusions: women with diabetes mellitus represent a high-risk pregnancy group, more work is needed to educate diabetic women, so CHD can be prevented and the outcomes of their pregnancy can be improved. Appropriate glycemic control before and during pregnancy may reduce CHD.

Factores de riesgo para cardiopatías congénitas: Estudio caso control

Resumen
Objetivos: investigar la prevalencia y los factores de riesgo en recién nacidos con cardiopatías congénitas.

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Genética;
Diabetes mellitus

Métodos: este estudio caso control incluyó 234.386 nacimientos desde enero del 2006 hasta junio del 2013, los cuales fueron evaluados y registrados según la metodología del Estudio Colaborativo Latinoamericano de Malformaciones Congénitas (ECLAMC) estableciendo el programa de vigilancia de defectos congénitos de Bogotá.

Resultados: de 234.368 pacientes fueron incluidos en el estudio, 277 fueron diagnosticados con cardiopatías congénitas. El defecto cardiaco más común fue la comunicación interventricular (13.7%) seguido por la comunicación interauricular (10.1%). Al evaluar los factores de riesgo se encontró que las madres con diabetes mellitus pregestacional tuvieron mayor riesgo de tener hijos con cardiopatías congénitas (OR 16.36 IC: 4.54–58.35) y que los pacientes con bajo peso al nacer (menor de 2.500 g) (OR: 4.13 IC: 3.13–5.44) y edad gestacional menor a 36 semanas (OR: 4.92 CI: 3–5.44) tenían mayor riesgo de ser diagnosticados con una cardiopatía congénita.

Conclusiones: las pacientes diabéticas en embarazo tienen mayor riesgo de que sus hijos desarrollen una cardiopatía congénita. Por lo anterior se necesita realizar un mayor trabajo tanto de educación como de seguimiento a las mujeres diabéticas, para así prevenir cardiopatías congénitas y disminuir el resigo de sus embarazos.

Introduction

The most common congenital anomalies (CA) are congenital heart defects (CHD), with a prevalence of 4 to 50 per 1,000 live-births in different studies, depending on the examination age and the sensitivity of the examination technique[1–6]. The birth prevalence of CHD was 1.2 per 1,000 live-births in a Colombian study of 44,985 children. This was based on the pediatric cardiology examination over four years in 11 colombian hospitals, using the Latin-American Collaborative Study of Congenital Malformations (ECLAMC) methodology, establishing the Bogota Birth Defects Surveillance and Follow-up Program (BBDSFP)[7].

Although the mortality associated with CHD has decreased, CHD remain one of the leading causes of infant/child mortality[8]. Over the past few years, there have been major breakthroughs in the understanding of genetic risk factors in CHD; however, there is relatively less information about the role of non-inherited modifiable factors in the origin of CHD and it is unknown in the majority of patients[9]. One of the most important risk factor is maternal diabetes mellitus, a chronic disease that is linked with difficult pregnancy and an increased prevalence of CA, perinatal morbidity and mortality in offspring. Studies show that the offspring of diabetic mothers have a five-fold increased incidence of CA compared to pregnancies in the general healthy population[10–13].

This study aimed to describe the prevalence and risks factors in the origin of CHD in a colombian population. The findings could be applied to current and future cardiac and perinatal care practice and to upcoming research.

Methods

Population

This case-control study included 234,386 births from January 2006 to June 2013 that were evaluated and registered in the BBDSFP based in ECLAMC, an international registry of congenital malformations and an exhaustive exploration of prenatal conditions for all malformed newborns identified and for paired controls. The newborns were evaluated during the first 48 hours postpartum[14].

Data were collected from different hospitals having high complexity level in Bogota D.C. (Table 1): Hospital Cafam; Clínica El Bosque; Clínica Veraguas; Hospital Kennedy; Hospital Universitario San Ignacio; Hospital Simón Bolívar; Hospital Central de la Policía; Hospital de Suba; Hospital Maternoinfantil de la Victoria; Hospital San José Infantil; Policlínico del Olaya, and Clínica Maternoinfantil de Saludcoop. All these institutions gave their approval before the study was conducted.

In this study it was take into account newborns with CHD from British Pediatric Association ICD-10 codes Q20.0 to Q25.4. It was defined as cases live newborns and stillborn weighing more than 500 g, who were born in one of the hospitals under observation (Table 1), and who presented with one or more of the selected CA. Multiple CA were defined

Table 1 Institutions from which data were collected.

Hospitals	Average number of annual newborns	Monthly average
Cafam	5,802	483.5
El Bosque	2,557	213.1
Veraguas	5,162	430.2
Kennedy	3,297	274.8
San Ignacio	2,726	227.2
Simón Bolívar	1,447	120.6
Policía	1,298	108.2
Suba	3,009	250.8
Materno Infantil	3,117	259.8
CMI 94	4,257	354.8
San José Infantil	4,465	372.1
Policlínico El Olaya	1,876	156.4

Table 2 Distribution of cardiovascular malformations in affected children.

Type of cardiac defects	n	%	Prevalence per 10,000 live-births
Acyanotic group			
Ventricular septal defect	38	13.72	1.62
Atrial septal defect	28	10.11	1.19
Tricuspid valve anomaly	9	3.25	0.38
Coarctation of the aorta	8	2.89	0.34
Pulmonary valve anomaly	5	1.81	0.21
Aortic valve anomaly	4	1.44	0.17
Patent ductus arteriosus	2	0.72	0.09
Other septal defects	2	0.72	0.09
Mitral valve anomaly	1	0.36	0.04
Cyanotic group			
Hypoplastic right heart	25	9.03	1.07
Tetralogy of Fallot	7	2.53	0.30
Transposition of great vessels	6	2.17	0.26
Single ventricle	6	2.17	0.26
Multiple congenital malformations	82	29.60	3.50
Non specified cardiopathy*	54	19.49	2.30
Total	277	100	11.82

* Non specified cardiopathy: patients that were diagnosed with CHD however the diagnosis of the cardiopathy was missing in the database.

as the presence of a major CA in two or more organ systems. Controls were defined as any live newborn that had been born in the same hospital during the same month as the case, and had no CA at time of birth. The controls were not sex-matched. The prevalence of birth was calculated taking into account the live newborns and the stillborn over 500 g which accomplished the inclusion criteria, over the total of newborns and stillborn over 500 g.

Exclusion criteria

The following was considered as an exclusion criterion: chromosomal abnormalities.

Risk factor evaluation

We evaluated whether the following variables were risk factors or not for isolated CHD: pre-conception maternal body mass index (BMI); maternal age; gestational age; newborn weight; smoking during pregnancy; hypothyroidism; consanguinity; gestational diabetes and diabetes mellitus.

Medication review

We evaluated medication used by the mother's cases each trimester of pregnancy.

Ethics approval and informed consent

We declare the local ethics committee accepted this project, and informed consent was obtained from the parents of all children participating in the study.

Analysis

Quantitative variables were compared using a t-test with a confidence interval of 95% and the qualitative variables were analyzed using an odds ratio with a confidence interval of 95%. It was used Microsoft Excel 2007 and Epicalc 2000 v1.02 for data management and statistical calculations, respectively.

Results

Baseline, socioeconomic status and other characteristics of the study population

A total of 277 cases of CHD were born in the area of study between the years 2006 and 2013 of which 77 were stillbirths, and were compared with 2,691 healthy control children, obtaining a case-control ratio of 1:9.71.

Distribution of congenital heart defects

Table 2 shows the distribution of cardiovascular malformations in cases. The prevalence of CHD was 11.82 per 10,000 live births. Of the 277 cases, the ventricular septal defect (VSD) was one of the most common malformations, followed by atrial septal defect (ASD). 29.60% of the CHD were associated with multiple congenital malformations.

Table 3 shows the distribution of multiple congenital malformations in newborns with CHD, the most common was defects or head malformations, in which we included macrocephaly, microcephaly, holoprosencephaly,

Table 3 Distribution of multiple congenital malformations.

Multiple malformations	n
Defects or head malformations	18
Kindney malformations	11
Congenital talipes	10
Ear malformations	9
Maxilar malformation	8
Imperforate anus	7
Syndactyly	6
Pulmonary defects	6
Hypospadias	5
Skull encephalic anomalies	4
Skin anomalies	4
Intestinal stenosis	2
Congenital limb defects	1

facial asymmetry, among others. Follow by kidney malformations and congenital talipes.

Table 4 shows the t-test results for the quantitative variables and the standard deviation in cases and controls. We found differences in weight and gestational age.

Risk factor analysis

Having any type of pre-gestational diabetes mellitus had an increased risk for the development of CHD (OR 16.36 CI: 4.54–58.35). It was found that low weight newborns (less than 2,500 g) (OR: 4.13 CI: 3.13–5.44) and a gestational age lower than 36 weeks

(OR: 4.92 CI: 3–5.44) increased the risk of presenting a CHD (Table 4).

However, pregnant women with a gestational age greater than 40 weeks (OR: 0.69 CI: 0.49–0.96) have lower risk of CHD presentation.

Some diseases and risk factors in pregnancy, such as passive and active smoking, hypothyroidism, maternal age, BMI, gestational diabetes and consanguinity were not associated with a higher risk of development of CHD.

Since we found a high correlation between diabetes and CHD we searched for the medication the mothers with diabetes were taking during pregnancy; the results are shown in Table 5 and Table 6.

Of the 6 newborns with CHD of the others' studies show the same results diabetic patients, three of them had an ASD, the others had a hypoplasic right heart, an aortic valve anomaly and one of them had multiple congenital

abnormalities which included transposition of great vessels with ventricular septal defect and cleft lip.

Discussion

This case-control study aimed to identify possible associations between risk factors and CHD in a colombian population. Risk factors, such as maternal gestational age and chronic diabetes mellitus, consanguinity, hypothyroidism, smoking, weight, gestational age, maternal age, and BMI. Some associations with high risk CHD were identified; noteworthy is the suggestion of diabetes mellitus.

CHD are the most common and serious structural birth defects worldwide (9 per 1,000 live-births). Our study showed a prevalence of 11.82 per 10,000 live-births of CHD, the most frequent was VSD (13.7%), followed by ASD (10.1%). A worldwide meta-analysis of congenital heart disease showed the same results; VSD was the one with the highest prevalence (2.62 per 1,000 live-births) followed by ASD (1.64 per 1,000 live-births). However, PDA was the third most prevalent defect in the meta-analysis and, in our study, the third most prevalent was hypoplastic right heart (9%)[15,16]. In our study, due to the high altitude in Bogota, PDA was only considered as a CHD if it needed closure with medical management or surgery. That is the reason why the prevalence of PDA is so low compared with the worldwide meta-analysis.

Analyzing the risk factors, we found a high association between diabetes and CHD (OR 16.36 CI: 4.54–58.35); this risk in our study is consistent with other studies that compare the anomaly rate in diabetic mothers[10–13,17–19]. Risk factors as weight less than 2,500 g, or a gestational age of less than 36 weeks, have an association with CHD; others' studies show the same results[7,20,21].

Our study did not find statically significant differences in the likelihood of CHD in some risk factors such as gestational diabetes mellitus, consanguinity, hypothyroidism, smoking, maternal age and BMI (Table 4).

The potential for the existence of cardiac abnormalities among the offspring of mothers with diabetes mellitus has been recognized for more than 50 years[16]. Our study finds a high correlation between pre-gestational diabetes mellitus and CHD. Although perinatal mortality has declined dramatically in diabetic pregnancies over the past years, most studies continue to show a higher mortality in these patients than in control populations[22,23]. studies from large regions in the United Kingdom encounter a high level of non-attendance at pre-conception care and poor glycemic control in diabetic mothers. However, the Dutch population

Table 4 T-test results for quantitative variables.

	Cases		Controls		
	Average	StD*	Average	StD	P
Weight	2,602.48	±744.34	3,005.07	±454.17	<0.05
Maternal age	26.77	±6.57	26.15	±6.51	>0.05
Gestational age	36.74	±3.75	38.28	±1.88	<0.05
BMI	22.53	±3.43	22.68	±3.76	>0.05

* Standard deviation

Table 5 Risk factor comparisons between cases and controls.

Variable	Cases		Controls		OR	(IC 95%)
	Yes	No	Yes	No		
Gestational Diabetes	8	269	85	2,876	1.00	0.48–2.09
Diabetes Mellitus	6	271	4	2,957	16.36	4.54–58.35
Consanguinity	3	177	27	1,779	1.11	0.33–3.71
Hypothyroidism	5	272	66	2,895	0.8	0.32–2.01
Smoking	26	242	242	2,686	1.19	0.77–1.82
Weight > 4,000 g	1	275	26	2,896	1.021	0.054–2.99
Weight < 2,500g	93	183	320	2,602	4.13	3.13–5.44
Gestational age > 40 wk	45	229	646	2,278	0.69	0.49–0.96
Gestational age < 36 wk	62	212	164	2,760	4.92	2.56–6.80
Maternal age > 35 yrs	40	234	370	2,552	1.17	0.82–1.67
Maternal age < 20 yrs	48	226	480	2,442	1.08	0.77–1.49
BMI < 16	1	110	9	1,520	1.53	0.19–12.2
BMI < 18.5	8	103	130	1,399	0.83	0.39–1.75
BMI > 25	23	88	202	1,226	1.58	0.97–2.57
BMI > 30	3	108	67	1,462	0.6	0.18–1.95

Table 6 Medication used by diabetic patients.

	Diabetic patient					
	1	2	3	4	5	6
NPH insulin	X	X		X	X	
Lispro insulin		X		X	X	
Insulin pump			X			
Oral metformin				X		X

shows that diabetic women who planned their pregnancies and have a good periconceptional glycemic control and an HbA1c of less than 7%, also have a significant increase in CA[3,24]. It is important to highlight that, according to the Latin American Diabetes Association (ALAD), the prevalence of diabetes in the world by 2030 is expected to be approximately 39.9 million cases, and almost 45% of those patients will ignore their condition[25].

Analyzing the medication that diabetic mothers take during pregnancy, we did not find a teratogenic drug. Insulin and metformin are safe to use in the gestational period as well as cephalexin, methyldopa and folic acid. However, the use of calcium carbonate in a high dose increased the risk for conotruncal heart defects[26–30].

According to the World Health Organization, diabetes mellitus prevalence in Colombia is 8,5%[31]. The National Health Survey[32] described that 96.5% of these diabetics are treated by a general practitioner, only 75% are advised to quit smoking, lose weight and control their blood glucose. Additionally, only 20% of diabetic patients measure their blood glucose at home. These has led us to believe that colombian diabetic pregnant woman do not have the follow-up they should.

Is noteworthy to describe different risk factors for CHD that we did not analyze in our study. A recent metanalysis in China[33] showed that mothers with advanced age (OR 2,6), cold or fever (OR 4,5), passive smoking (OR 2,7), noise exposure (OR 3) and radiation exposure (OR 2,9) were prone to have children with cardiac defects.

The study limitations were that newborns were only followed 48 hours after delivery, that prenatal echocardiography was not available for all the patient's mothers during pregnancy, and that echocardiographic results are operator dependent.

Conclusions

Women with diabetes mellitus represent a high-risk pregnancy group. The incidence of diabetes mellitus is increasing, especially at younger ages; therefore, the number of pregnant diabetic women will also continue to increase. Our study found a high correlation between diabetic mothers and CHD. Since 1980 the literature has described an association between poor glycemic control and high-risk pregnancies. Hence, we believe that more work is needed to educate diabetic women, so CHD can be prevented and the outcomes of their pregnancy can be improved. Diabetic women who are trying to get pregnant should have a strict glycemic control, especially in the first trimester, since pregnancies with poor first trimester control are more at risk of complex forms of CHD[16,34].

Ethics approval

This study was conducted with the approval of the Comité de Investigaciones y Ética de la Facultad de Medicina y el Hospital Universitario San Ignacio.

Competing interests

None.

Contributors

None.

Acknowledgements

We would like to thank all the health services that permitted us to acquire the data that made this project possible: Hospital Cafam, Clínica El Bosque, Clínica Veraguas, Hospital Kennedy, Hospital Universitario San Ignacio, Hospital Simón Bolívar, Hospital Central de la Policía, Hospital de Suba, Hospital Maternoinfantil de la Victoria, Hospital San José Infantil, Policlínico del Olaya and Clínica Maternoinfantil de Saludcoop.

References

1. Czeizel AE, Kamarás J, Balogh O, Piloute L. Incidence of congenital heart defects in Budapest. Acta Paediat Acad Sci Hung. 1972;13:191–200.
2. Hoffman JI, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol. 2002;39:1890–900.
3. Hoffman JI, Kaplan S, Liberthson RR. Prevalence of congenital heart disease. Am Heart J. 2004;147:425–39.
4. Calzolari E, Garani G, Cocchi G, Magnani C, Rivieri F, Neville A, et al. Congenital heart defects: 15 years of experience of the Emilia-Romagna Registry (Italy). Eur J Epidemiology. 2003;18:773–80.
5. Reller MD, Strickland MJ, Riehle-Colarusso T, Mahle WT, Correa A. Prevalence of congenital heart defects in Metropolitan Atlanta. J Pediatr. 2005;153:807–13.
6. Dolk H, Loane M, Garne E. Congenital heart defects in Europe: Prevalence and perinatal mortality. Circulation. 2011;123:841–9.
7. Baltaxe E, Zarante I. Prevalencia de malformaciones cardiacas congenitas en 44.985 nacimientos en Colombia. Archivos de Cardiologia de México. 2006, 263-8.
8. Boneva RS1, Botto LD, Moore CA, Yang Q, Correa A, Erickson JD. Mortality associated with congenital heart defects in the United States: Trends and racial disparities 1979-1997. Circulation. 2001;103:2376–81.
9. Jenkins KJ1, Correa A, Feinstein JA, Botto L, Britt AE, Daniels SR. Noninherited risk factors and congenital cardiovascular defects: Current knowledge: A scientific statement from the American heart association council on cardiovascular disease in the young. Circulation. 2007;115:2995–3014.
10. Macintosh MC. Perinatal mortality and congenital anomalies in babies of women with type 1 or type 2 diabetes in England. Wales and Northern Ireland: pop,ulation based study. BMJ. 2006:1–6.
11. Vereczkey A, Gerencsér B, Czeizel AE, Szabó I. Association of certain chronic maternal diseases with the risk of specific congenital heart defects: a population-based study. Eur J Obstet Gynecol Reprod Biol. 2014;182:1–6.
12. Garne E, Loane M, Dolk H, Barisic I, Addor MC, Arriola L, et al. Spectrum of congenital anomalies in pregnancies with pregestational diabetes. Birth Defects Res A Clin Mol Teratol. 2012;94:134–40.
13. Garg S, Sharma P, Sharma D, Beherva V, Durairaj M, Dhali A. Use of fetal echocardiography for characterization of fetal cardiac structure in women with normal pregnancies and gestational diabetes mellitus. J Ultrasound Med. 2014;33:1365–9.
14. Castilla EE, Orioli IM. ECLAMC: the Latin American collaborative study of congenital malformations. Community Genetics. 2004;7:76–94.
15. Van der Linde D, Konings EE, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJ. Birth prevalence of congenital heart disease worldwide: A systematic review and meta-analysis. J Am Coll Cardiol. 2011;58:2241–7.
16. Kornosky JL, Salihu HM. Getting to the heart of the matter: epidemiology of cyanotic heart defects. Pediatr Cardiol. 2008;29:484–97.
17. Lisowski LA, Verheijen PM, Copel JA, Kleinman CS, Wassink S, Visser GH, et al. Congenital heart disease in pregnancies complicated by maternal diabetes mellitus. Herz. 2010;35:19–26.
18. Correa A, Gilboa SM, Besser LM, Botto LD, Moore CA, Hobbs CA, et al. Diabetes mellitus and birth defects. Am J Obstet Gynecol. 2008;199:237e1–9e.
19. Abu-Sulaiman RM, Subaih B. Congenital heart disease in infants of diabetic mothers: echocardiographic study. Pediatr Cardiol. 2004;25:137–40.
20. Patel SS, Burns TL. Nongenetic risk factors and congenital heart defects. Pediatric Cardiology. 2013;34:1535–55.
21. Casson IF, Clarke CA, Howard CV. Outcomes of pregnancy in insulin dependent diabetic women: Result of a five year population cohort study. Br Med J. 1997;315:275–8.
22. Evers IM, de Valk HW, Visser GHA. A nationwide prospective study on the outcome of pregnancies in women with type 1 diabetes mellitus: Do planned pregnancies result in better pregnancy outcomes? Diabetologia. 2001;44 Suppl 1:A42.
23. Csáky-Szunyogh M, Vereckey A, Kóza Z, Balázs Gerencsér, Andrew E, Czeizel. Risk and protective factors in the origin of conotruncal defects of heart - a population-based case-control study. Am J Med Genet A. 2013:2444–52.
24. Evers IM, Bos AM, Aalders AL. Zwangershcap bij vrouwem met diabetes mellitus type-1: nog steeds maternale en perinatale complicaties, ondanks geode bloedglucoseregulatie. Ned Tijdschr Geneeskd. 2000;144:804–9.
25. Aschner P, Mendicil D, Pinzón JB, et al. Guías ALAD sobre diagnóstico, control y tratamiento de la diabetes mellitus tipo 2 con medición basada en la evidencia. Epidemiología de la diabetes tipo 2 en Latinoamérica. 2013:17–24.
26. Shaw GM, Carmichael SL, Yang W, et al. Periconceptional nutrient intakes and risk of conotruncal defects. Birth defects. Res A Clin Mol Teratol. 2010;88:144–51.
27. De Santis M, Carducci B. Drug induced congenital defects: strategies to reduce the incidence. Drud Safe. 2001;24:889–901.
28. Mirela E, Sabo A. Teratogenicity of antibacterial agents. Coll Antropol. 2008;32:919–25.
29. Kalaĭdzhieva M, Popivanova A, Doĭcheva E, Nikolov A, Dimitrov A. Maternal insulin-dependent diabetes and congenital malformations in the newborn. Akush Ginekol (Sofiia). 2003;42:3–5.
30. Naganda K, Somsbhra D, Kanagasabai S. Oral hypoglycemic agents in pregnancy: an update. J Obset Gynacol India. 2013;63:82–7.
31. Statistics by topic: demography and population. Available at: http://www.dane.gov.co/index.php/estadisticas-por-tema/demografia-y-poblacion.[Accessed 25 Feb 2019].
32. González JC, Walker JH, Einarson TR. Cost-of-illness study of type 2 diabetes mellitus in Colombia. Rev Panam Salud Publica. 2009;26:55–63.
33. Liu Y, Zhu B, Zhou L, He MY, Xu Y, et al. Risk factors for congenial heart disease in chinese neonates: a Meta analysis. Zongguou Dang Dai Er Ke Za Zhi. 2017;19:754–8.
34. Mitanchez D. Management of infants born to mothers with gestational diabetes. Paediatric environment. Diabetes Metab. 2010;36:587–94.