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Characterization of prenatal exposure variables in a group of children aged 0-5 years with congenital heart defect treated in Cali, Colombia. The importance of folic acid

Caracterización de la exposición prenatal de un grupo de niños de 0 a 5 años con cardiopatía congénita atendidos en Cali, Colombia. La importancia del ácido fólico

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Abstract

Introduction: Congenital heart defects (CHD) have an estimated prevalence of 4 to 9 cases per 1 000 births, and they have a significant impact on child morbidity and mortality. This prevalence variability has been attributed to regional differences in terms of genetic and environmental factors, among others.
Objective: To obtain data on prenatal exposure variables of patients with CHD treated in Cali, Colombia.
Materials and methods: A survey was administered to the mothers of 30 children aged 0 to 5 years with CDH treated in 2 health institutions of Cali, Colombia. The instrument was oriented to collect data on multiple prenatal exposure variables, and data collected were entered into an Excel database in order to analyze them using descriptive statistics.
Results: Several types of exposure potentially associated with having CHD were found, including altered body mass index, inadequate administration of folic acid, and being exposed to X-rays, vitamin A, alcohol and tobacco.
Conclusion: Insufficient or untimely administration of folic acid could facilitate the development of teratogenic effects of oxidizing agents. Therefore, education programs on the importance of a proper intake of folic acid and the risks derived from exposure to teratogenic agents during pregnancy should be provided to all pregnant women in Cali to reduce the incidence rate of CHD in the city.
Keywords: Congenital Heart Defects; Environmental Exposure; Congenital Abnormalities (MeSH).

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Resumen

Introducción. Con una prevalencia estimada de 4 a 9 casos por cada 1 000 nacimientos, las cardiopatías congénitas (CC) tienen gran impacto en la morbimortalidad pediátrica. La variabilidad de prevalencia se ha atribuido a diferencias regionales en cuanto a factores genéticos, ambientales, entre otros.
Objetivo. Obtener datos sobre variables de exposición prenatales de pacientes con CC atendidos en Cali, Colombia.
Materiales y métodos. Se aplicó una encuesta a las madres de 30 pacientes de 0 a 5 años con CC atendidos en 2 clínicas de alta complejidad (tercer y cuarto nivel) de Cali. La encuesta estaba orientada a múltiples variables de exposición y la información recolectada fue digitalizada en una base de datos en el programa Microsoft Excel para hacer un análisis estadístico descriptivo.
Resultados. Se evidenciaron varias exposiciones potencialmente asociadas a CC, tales como índice de masa corporal alterado, administración inadecuada de suplementos de ácido fólico y exposición a vitamina A, rayos X, alcohol y cigarrillo.
Conclusión. El consumo insuficiente o inoportuno de ácido fólico podría facilitar la generación de efectos teratogénicos de sustancias oxidantes. Por lo tanto, se debe educar a las mujeres de Cali sobre la importancia de una ingesta adecuada de ácido fólico y sobre los riesgos de la exposición a agentes teratogénicos durante el embarazo para reducir las tasas de incidencia de CC en esta ciudad.
Palabras clave: Cardiopatías congénitas; Exposición a riesgos ambientales; Anomalías congénitas (DeCS).

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Introduction

Congenital anomalies are found in 2-3% of newborns and constitute a major public health problem; in Colombia, the most common anomalies of this type include alterations of the limbs, central nervous system defects and congenital heart disease (CHD).[1] Given that CHD have the greatest impact, since 2010, pulse oximetry has been implemented in the U.S. as a routine screening method on all live newborns for early detection of congenital heart defects associated with hypoxia in the neonatal period.[2]

Some studies associate the occurrence of CHD with teratogenic agents,[3-5] and others, based on animal models extrapolated to humans, argue that the consumption of folic acid (also known as folate) during the first 3 weeks of pregnancy prevents heart disease caused by exposure to teratogens.[6-7] In this sense, it is known that initiating folic acid supplementation in humans one month prior to pregnancy reduces the incidence of neural tube defects by more than 70%;[8] furthermore, there is epidemiological evidence that supplementing mothers with this vitamin protects the babies against various types of CHD.[9]

The aim of this study was to obtain data on prenatal exposure variables of CHD patients treated in Cali, Colombia. Consequently, this research is the first step towards improving the understanding of the multiple factors related to CHD in the local context.

Materials and methods

A descriptive case series study was conducted using a random sample of 30 patients under 6 years of age with CHD treated in 2 institutions of Cali: DIME Clínica Neurocardiovascular (institution 1) and Clínica Versalles (institution 2). Isolated ductus arteriosus cases were excluded because only newborns without gestational age or disease status restriction were included in the study, as it is known that, regardless of exposure to other factors, gestational age and the presence of respiratory distress syndrome can affect ductal closure.[10]

Patients treated between September 2014 and November 2015 were selected for this study. In the case of institution 1, which is a reference center for the diagnosis and management of cardiovascular diseases, the database of echocardiograms performed there was reviewed and the mothers of CHD patients born in the past 5 years were contacted by phone to invite them to participate in the study; calls were made in chronological order, that is beginning with the patient most recently treated. Once the mother agreed to participate, an appointment was made with her and the patient to formally carry out the informed consent process and administer the survey to the mother.

In order to select the patients in institution 2, which is a tertiary care center with the highest number of births in the city, all the care staff of the Obstetrics Service and the Newborn Intensive Care Unit were informed of the study, so that when new cases of newborns with CHD confirmed by echocardiogram were diagnosed, they informed the study staff, who also asked daily if there were any new cases, thus allowing an active search. When the CHD were confirmed, the informed consent process and the mother's survey were formally conducted. No patients were captured by screening with pulse oximetry.

The administered survey was an extensive instrument of more than 90 pages, validated in previous original studies and designed by the research groups Congenital and Perinatal Malformations, Medical Genetics and Dysmorphology (MACOS by its acronym in Spanish) and Epidemiology and Population Health (GESP by its acronym in Spanish). It sought to find out multiple socio-demographic and exposure variables such as drinking water, medicines, cigarettes, alcohol and other psychoactive substances, as well as the history of diseases and X-ray studies. At this point, it is worth noting that there may be memory bias when answering this type of survey.

The collected data were digitized in a Microsoft Excel sheet and a univariate and bivariate descriptive statistical analysis was performed using relative frequency distributions (%) presented in tables to describe the exposure characteristics found.

This study was approved by the Institutional Committee for the Review of Human Ethics of the Faculty of Health of the Universidad del Valle by means of approval act No. 04013 of April 5, 2013. Moreover, the principles of the Declaration of Helsinki[11] and the regulations of Resolution 8430 of 1993 of the Colombian Ministry of Health were followed.[12]

Results

Socio-demographic characterization

Of the 30 cases, 24 were captured in institution 1 and 6 in institution 2. The births took place in 13 health institutions, mostly in the Hospital Universitario del Valle and the Clínica Versalles, which means that 16 of the patients were born in one of these 2 institutions.

The sample studied was composed of 19 boys (63.33%) and 11 girls (36.67%). Regarding health insurance, 46.66% of the mothers were enrolled in the subsidized regime and 53.33% in the contributory regime, and 56.66% of them lived in Cali during the periconceptional period (3 months before and 3 months after the approximate date of conception or fertilization) (Table 1).

Among the mothers who lived in Cali during their periconceptional period, most resided in the central and eastern areas (Aguablanca district): 23.5% in commune 14 and 17.6% in commune 9; the remaining mothers lived in different communes during this period, that is, they were distributed without constituting aggregates. Both institutions where the study was conducted are in commune 2.

Table 1. Socio-demographic characteristics of the study cases.

Characteristics		n (%)
Sex	Women	11 (36.67%)
	Men	19 (63.33%)
Place of residence during the periconceptional period	Cali	17 (56.66%)
	Outside Cali	13 (43.33%)
Health Care System	Contributive	16 (53.33%)
	Subsidized	14 (46.66%)

Source: Own elaboration.

Characterization of the exposure

20 of the 30 pregnancies were not planned, and, on average, the mothers found out about their status during the 7th week. An average of 8 prenatal check-ups was obtained, and ultrasound studies detected some fetal structural abnormality in only 2 cases; no invasive prenatal diagnostic study was performed for any of these cases. In a third case, the ultrasound reported a placental abnormality.

Table 2 shows and describes the types of heart disease found in the patients included in the series, while Tables 3, 4 and 5 summarize the most relevant maternal exposures found in the research.

Table 2. Characterization of the patients included in the research.

Case	Age at study entry	Heart disease	Associated abnormalities
1	1 day	Transposition of the great arteries	None
2	4 months	Double atrioventricular canal, single ventricle, transposition of the great arteries	Complete situs inversus, intestinal malrotation
3	2 months	Tricuspid insufficiency	None
4	7 days	Tetralogy of Fallot, patent ductus arteriosus, interatrial communication and hypoplasia of the valve, trunk and branches of the lungs	None
5	1 day	Ventricular septal defect	Right preauricular sinuses, abnormal hand and foot dermatoglyphics, clinodactyly, hypoplasia of the middle phalanx of the fifth digit of the left hand
6	1 day	Ventricular septal defect, patent foramen ovale	Down facies (Down syndrome confirmed by karyotype)
7	5 days	Left lower pulmonary vein stenosis, ventricular septal defect, patent ductus arteriosus	Low-set ears, over-folded ears, prominent antihelix, hypoplastic helix crus, protruding cheekbones, microstomia, hands in trisomy, prominent heel (trisomy 18 confirmed by karyotype)
8	1 day	Complete atrioventricular canal	None
9	20 days	Patent ductus arteriosus, patent foramen ovale, mild to moderate mitral regurgitation, mild tricuspid regurgitation	None
10	2 days	Tricuspid atresia, right ventricular hypoplasia, pulmonary atresia	None
11	2 months	Truncus arteriosus	Hirsutism (on the face, back and limbs), absent earlobe, wide nasal bridge, micrognathism, micropenis.
12	22 days	Double outlet right ventricle, severe pulmonary stenosis, transposition of the great arteries	None
13	5 days	Atrioventricular valve dysplasia, moderate tricuspid regurgitation, situs inversus	None
14	1 month	Dysplastic pulmonary valve with insufficiency and stenosis	None
15	6 months	Ostium secundum atrial septal defect, patent ductus arteriosus	Epicanthal fold, short nose, smooth philtrum, anteverted nostrils
16	1 year	Ventricular septal defect, patent foramen ovale	Down facies (Down syndrome confirmed by karyotype), hypothyroidism
17	1 month	Tetralogy of Fallot	Low-set ears, myelomeningocele, hydrocephalus, shortening of the second left metatarsal bone, abnormal dermatoglyphics
18	4 years	Interatrial communication	Esophageal atresia, neonatal teeth (two incisors), big, protruding ears
19	4 years	Double superior vena cava system, persistent left superior vena cava, dilated coronary sinus	Café-au-lait spots (one spot of 5cm in the lower right quadrant of the abdomen)
20	2 years	Ventricular septal defect	Delayed psychomotor development, bilateral hydronephrosis, protuding forehead, arched eyebrows
21	2 years	Subvalvular aortic stenosis, tricuspid but functionally bicuspid aortic valve, aortic vascular ring in the descending thoracic aorta without coarctation	None

Table 2. Characterization of the patients included in the research. (continued)

Case	Age at study entry	Heart disease	Associated abnormalities
22	1 month	Single atrioventricular connection through a central atrioventricular valve, double-outlet right ventricle, blood vessels in abnormal position, right ventricular hypoplasia, right anterior aorta and left posterior pulmonary aorta, interatrial communication, single atrium, lack of interventricular septum, dilated left ventricle, hypoplastic pulmonary artery, patent ductus arteriosus, single atrioventricular valve, right aortic arch, tricuspid pulmonary atresia with severe infundibular and pulmonary stenosis	Right isomerism, esophageal atresia
23	1 day	Ostium secundum atrial septal defect, moderate mitral regurgitation	Frontal hemangioma extending towards the right eye, anteverted nostrils, inverted nipples, megabladder, bilateral hydronephrosis, large, thick-walled, partitioned bladder mass, anasarca, anal atresia, urethral meatus agenesis, probable urogenital sinus, lumbar hemivertebra
24	2 days	Right ventricle hypoplasia,pulmonary atresia	None
25	2 years	Supracardiac pulmonary anomalous venous connection, interatrial communication, persistent left superior vena cava.	Café au lait spot on right shoulder with a diameter of 3cm, short nose, barely visible nasal tip, anteverted nostrils, long philtrum, protruding cheekbones, left cryptorchidism
26	5 years	Ventricular septal defect, interatrial communication, pulmonary stenosis	Seizures, repeated respiratory infections, strabismus, flattened cervical vertebrae, delayed psychomotor development, self-injury (of the tongue), dolicocephaly, big ears, thick lips, pectus excavatum, right cryptorchidism, hypotonia
27	4 years	Tetralogy of Fallot, mild stenosis at the origin of the right pulmonary branch	Atopic dermatitis, mild y-shaped syndactyly between toes 2 and 3, including penis.
28	2 years	Pulmonary stenosis, patent foramen ovale	Neonatal jaundice, wide nose, small café-au-lait spots
29	2 years	Ebstein anomaly, tricuspid insufficiency	Left pyelectasis, two café-au-lait spots <1cm on the abdomen
30	2 years	Coarctation of the aorta, interatrial communication	Agenesis of the corpus callosum

Source: Own elaboration.

Table 3. Periconceptional exposures found in this study.

Case	Exposure in the 3rd month before conception	Exposure in the 2nd month before conception	Exposure in the 1st month before conception	Exposure in the 1st month after conception	Exposure in the 2nd month after conception	Exposure in the 3rd month after conception
1	None	Warfarin	Alcohol (beer, rum, aguardiente, whisky)	Acetaminophen, warfarin, alcohol (beer, rum, aguardiente, whisky)	Warfarin, alcohol (beer, rum, aguardiente, whisky)	Warfarin, alcohol (beer, rum, aguardiente, whisky)
2	Smoker at home	Smoker at home	Smoker at home	Smoker at home	Acetaminophen, smoker at home	Smoker at home
3	NPH and aspart insulin, smoker at home	NPH and aspart insulin, smoker at home	NPH and aspart insulin, smoker at home	NPH and aspart insulin, smoker at home	NPH and aspart insulin, smoker at home	NPH and aspart insulin, smoker at home
4	Contraceptive injection, smoker at home	Contraceptive injection, smoker at home	Contraceptive injection, smoker at home	Contraceptive injection, metoclopramide, acetaminophen	Contraceptive injection	Contraceptive injection
6	None	Acetaminophen	None	Alcohol (beer)	None	Acetaminophen
7	None	None	None	Aspirin, metoclopramide	Aspirin, metoclopramide	Aspirin

Table 3. Periconceptional exposures found in this study. (continued)

Case	Exposure in the 3rd month before conception	Exposure in the 2nd month before conception	Exposure in the 1st month before conception	Exposure in the 1st month after conception	Exposure in the 2nd month after conception	Exposure in the 3rd month after conception
10	None	None	None	None	None	Acetaminophen, metoclopramide
11	None	None	None	Acetaminophen	Acetaminophen, alcohol (rum, aguardiente, whisky)	None
12	Acetaminophen	Acetaminophen	Acetaminophen	Acetaminophen	Acetaminophen	Acetaminophen
13	Alcohol (beer), marihuana, smoker at home	Alcohol (beer), marihuana, smoker at home	Alcohol (beer), marihuana, smoker at home	Alcohol (beer), marihuana, smoker at home	Levothyroxine, Alcohol (beer), marihuana, smoker at home	Levothyroxine, marihuana, smoker at home
14	Smoker at home, alcohol (beer, rum, aguardiente, whisky)	Smoker at home, alcohol (beer, rum, aguardiente, whisky)	Acetaminophen, smoker at home, alcohol (beer, rum, aguardiente, whisky)	Acetaminophen, omeprazole, smoker at home, alcohol (beer, rum, aguardiente, whisky)	Acetaminophen, omeprazole, smoker at home	Smoker at home
15	Smoker at home	Smoker at home	Smoker at home	Smoker at home	Acetaminophen, smoker at home	Smoker at home
17	None	Smoker at home	Smoker at home	Smoker at home	Smoker at home	Smoker at home
18	None	None	None	Acetaminophen	Acetaminophen	Levothyroxine
19	Alcohol (beer), smoker at home	Alcohol (beer), smoker at home	Alcohol (beer), smoker at home	Acetaminophen, smoker at home	Ovules, acetaminophen, smoker at home	Smoker at home
20	Acetaminophen	Acetaminophen	Acetaminophen	None	None	None
21	Acetaminophen, smoker at home	Acetaminophen, smoker at home	Acetaminophen, smoker at home, alcohol (beer, rum, aguardiente, whisky)	Acetaminophen, metoclopramide, smoker at home, alcohol (beer, rum, aguardiente, whisky)	Smoker at home, misoprostol	Smoker at home
22	None	None	None	Alcohol (whisky cream)	None	None
24	None	None	None	None	None	Acetaminophen
25	None	Acetaminophen	Acetaminophen	Acetaminophen, alcohol (beer)	None	None
27	None	None	None	None	Acetaminophen	Acetaminophen
28	Smoker at work	Smoker at work	Smoker at work	Acetaminophen, smoker at work	Acetaminophen, smoker at work	Acetaminophen, smoker at work
29	None	None	None	None	Magnesium sulfate, acetaminophen	Magnesium sulfate, acetaminophen

Source: Own elaboration.

Table 4. Maternal diseases and pregnancy exposures.

Disease/exposure	n (%)
Pregestational diabetes	1 (3.33%)
Gestational diabetes	1 (3.33%)
Chronic hypertension	1 (3.33%)
Gestational hypertension	3 (10%)
Hypothyroidism	1 (3.33%)
Hypoglycemia	1 (3.33%)
Pregestational Body Mass Index >24.9	10 (33.33%)
Pregestational body mass index <18.5	1 (3.33%)
X-rays without protection	4 (13.33%
Folic acid supplementation: absent or initiated after the first month of pregnancy	18 (60.0%)
Vitamin A	1 (3.33%) (exposure during the second and third trimesters of pregnancy)
Warfarin	1 (3.33%)

Source: Own elaboration.

Table 5. Non-therapeutic maternal exposures.

Exposure	n (%)
Active smoking	0 (0%)
Passive smoking	11 (36.66%)
Alcohol *	9 (30%)
Marihuana *	1 (3.33%)
Misoprostol	1 (3.33%)
Untreated river water	3 (10%)
Consumption of boiled river water	4 (13.33%)
Consumption of untreated well water	2 (6.66%)

* The questionnaire included the quantification of alcohol and marijuana consumption; however, the mothers did not remember or could not specify the amount.

Source: Own elaboration.

Discussion

Socio-demographic aspects

41% of the mothers who lived in Cali during their periconceptional period resided in communes 14 and 9, which are composed of neighborhoods in strata 2 and 3 (Table 6).

In commune 14, 68.4% of the houses are classified as stratum 1 and 31.6% as stratum 2; 17.7% of office machinery factories (telephones, computers, printers, photocopiers, video projectors, guillotines, etc.), 11.8% of automotive industries and 10.7% of electricity, gas and water suppliers of the city are located in this place. Some of its main problems are the lack of adequate green areas and environmental education programs, and inadequate solid waste disposal.[13]

Table 6. Socioeconomic strata in Colombia according to the National Administrative Department of Statistics.

Stratum	Description
1	Low-low. Beneficiaries of home utility subsidies.
2	Low. Beneficiaries of home utility subsidies.
3	Middle-low. Beneficiaries of home utility subsidies.
4	Middle. They are not beneficiaries of subsidies, nor do they pay surcharges; they pay exactly the amount that the company defines as the cost for providing home utilities.
5	Middle-high. They pay surcharges (contribution) on the value of home utilities.
6	High. They pay surcharges (contribution) on the value of home utilities.

Source: Elaboration based on the data by National Administrative Department of Statistics.[14]

On the other hand, the commune 9 is characterized because 10% of the households are stratum 1, 20% are stratum 2, and 70% are stratum 3. This place concentrates 32.69% of the recycling centers and 25% of the tanneries and centers of preparation of leathers (footwear) of the city.[13]

These findings explain the need for a specific and detailed analysis of risk factors associated with congenital anomalies in these geographical areas.

Exposure aspects

An unplanned pregnancy increases the chances of risk exposure during the periconceptional period, as a woman who is not aware of her condition continues to engage in behaviors she might not have if she knew. In addition, late pregnancy awareness does not allow for the timely consumption of the necessary micronutrients. In this study, 66.66% of the pregnancies were unplanned.

Quality of prenatal care

The mothers assisted, on average, to 8 prenatal checkups, which is an acceptable number. All of them underwent at least 1 obstetric ultrasound, although this examination only detected anomalies in 3 cases; thus, considering that ultrasound findings in one of the cases revealed a placental anomaly, only 2 patients were diagnosed with fetal structural anomalies. It should be noted that the 2 mothers diagnosed with fetal structural anomalies belong to the contributory regime, which means that some fetal structural anomaly was detected in 12.5% of the mothers in the contributory regime and none in the mothers enrolled in the subsidized regime. This may suggest that there is less access to timely and quality ultrasound for the mothers in the latter, as previously reported.[15]

Maternal hypertension

Chronic maternal hypertension has been associated with CHD (OR: 1.81, 95% CI: 1.61-2.03),[16] specifically with ventricular septal defects, common atrioventricular

canal defect and truncus arteriosus. It has been found that there is increased prevalence of non-critical CHD in children of women who develop preeclampsia after the 34th week, and that the prevalence of critical and non-critical heart disease increases in children of women who develop preeclampsia before the 34th week.[17] Significant associations between maternal hypertension and CHD in general have been observed for treated (RR: 2, 95% CI: 1.5-2.7) and untreated patients (RR: 1.4, 95% CI: 1.2-1.7), as well as for hypertension (RR: 1.8, 95 CI%: 1.5-2.2).[18]

This study found that 4 of the mothers had hypertension: 1 of them had chronic hypertension and her child presented tricuspid insufficiency, while the other 3 mothers had gestational hypertension with onset before the 34th week and their children presented syndromic cardiopathies.

Maternal diabetes

It is well known that the incidence of congenital abnormalities, including heart disease, is high in children of diabetic mothers.[5] Traditionally, it was thought that this increased risk was limited to patients with diabetes at the time of conception; however, it has been suggested that hyperglycemia caused by gestational diabetes may also influence cardiac development, which has been particularly associated with abnormalities such as patent ductus arteriosus, pulmonary stenosis and interventricular septal hypertrophy.[19] Likewise, Ornoy[20] proposes hyperglycemia-induced oxidative stress as a teratogenic mechanism of maternal diabetes.

This study also found that 2 of the mothers had diabetes: the first, mother of a patient with isolated tricuspid insufficiency, had preconceptional type 1 diabetes —which is associated with CHD (OR: 4.65, 95%CI: 4.13-5.24),[16] specifically coarctation of the aorta,[4] while the second, mother of a patient with Ebstein's anomaly and tricuspid insufficiency, had gestational diabetes. It is noteworthy that alterations in the tricuspid valve were observed in 3 of the 4 cases of maternal hypertension and in the 2 cases of gestational diabetes.

Maternal thyroid disease

Studies such as Liu *et al.*[16] have associated thyroid disorders with CHD (OR: 1.45, 95%CI: 1.26-1.67). In the present investigation, 1 of the mothers had hypothyroidism and her child (case 18) presented ventricular septal defect.

Maternal hypoglycemia

In animal models, hypoglycemia has been found to be potentially teratogenic during embryogenesis.[8] This study found that 1 of the mothers had hypoglycemia and her child had subvalvular aortic stenosis, tricuspid (but functionally bicuspid) aortic valve and aortic vascular ring in the descending thoracic aorta without coarctation.

Maternal body mass index

Previous studies have reported an association between maternal body mass index (BMI) and the occurrence of CHD; in general, the higher the BMI, the higher the OR for CHD.[21] Low maternal weight, on the other hand, appears to increase the risk for aortic stenosis.[22]

This study found that 10 of the mothers started the pregnancy with BMI above normal values (>24.9) and 1 with BMI lower than normal values (<18.5), which may indicate that BMI alterations are an important factor for the development of heart disease in the study population.

Exposure to X-rays

It has been found that the risk of inducing embryonic death or congenital anomalies after irradiating a newly fertilized egg with the usual range of doses used in diagnostic radiology is very low compared to the spontaneous risks. However, these findings are not considered a reason not to take precautions when possible, in part due to the possibility of epigenetic alterations.[23] In this sense, Ornoy[20] proposes that the teratogenic mechanism of ionizing radiation is the induction of oxidative stress.

This research found that 4 of the mothers underwent x-ray studies during pregnancy without protection, and that 3 of these children had non-syndromic heart disease and 1 had syndromic heart disease.

Exposure to tobacco

Mothers who smoke during the first trimester have been reported to be at increased risk of having children with CHD (OR: 1.16, 95%CI: 1.08-1.24). A dose-dependent effect and a very strong association have also been observed in some specific defects such as pulmonary valve disease, pulmonary artery anomalies and isolated interatrial communication.[24] In this sense, passive periconceptional exposure to tobacco has been established as an independent risk factor for heart disease[25,26] and the teratogenic mechanism of tobacco is the induction of oxidative stress.[20]

None of the mothers in this study smoked during pregnancy, so there appears to be an awareness of the potential dangers of smoking among them, but this was not the case for passive smoking exposure, as 36.66% of them were exposed.

Exposure to alcohol

Maternal alcohol consumption is known to cause multiple birth defects included in fetal alcohol syndrome (FAS), among them, heart disease. Only 10% of those affected with alcohol embryopathy meet all the criteria for FAS, while the remaining 90% fall somewhere else on the spectrum.

Multiple studies have shown that maternal alcohol consumption increases the risk of CHD[3,16,27] and teratogenic mechanisms include disruption of midline expansion;[28,29] apoptosis and alteration of neural crest and anterior precordal mesoderm cell migration;[30-32] disruption of several signaling pathways such as shh, fgf8, foxa2 and goosecoid;[29,33] and induction of oxidative stress.[20,34] This study found that 30% of the mothers consumed some alcohol, perhaps indicating a lack of awareness that there is no safe time or dose for alcohol consumption during pregnancy.

Folic acid intake

Folate is necessary for the synthesis of purines and pyrimidines, and therefore, it is important for proper cell proliferation. This micronutrient is also necessary for the synthesis of S-Adenosyl methionine, the main donor of methyl groups, and for adequate epigenetic regulation.[35,36]

It is well known that starting folic acid supplementation 1 month before pregnancy reduces over 70% of neural tube defects.[8] Worldwide, it is recommended that all women who may become, plan to become, or are pregnant take a daily supplement of 0.4mg to 0.8mg (400-800µg) of this vitamin.[37]

On the other hand, by using animal models extrapolated to humans, it has been found that the consumption of folic acid during the first 3 weeks of pregnancy prevents heart disease due to teratogenic exposure.[6,7] There is epidemiological evidence in humans that maternal folate supplementation is associated with a significant decrease in the risk of CHD (RR: 0.72; 95%CI: 0.63-0.82).[9]

This study found that only 10% of mothers started folic acid supplementation 1 month before conception, 30% during the first month of pregnancy, 36.66% after the first month, 16.66% did not receive supplementation and 6.66% took some multivitamin after the first month of pregnancy. The methodology used does not allow stating that the folate consumed did not have a protective effect against congenital anomalies. However, it showed that a high percentage (60%) of mothers did not consume it in the way recommended to generate a protective effect against neural tube defects nor in the way theoretically suggested by animal studies to achieve a protective effect against heart disease. Thus, although 83.34% of mothers received folic acid supplementation, it could only have a potential protective effect against neural tube defects and heart disease in the 10% who initiated it 1 month before conception, and it only had a potential protective effect against CHD in the 30% who initiated it during the first month of conception.

It is very interesting that the teratogenic mechanism of several of these factors (diabetes, X-rays, cigarettes, alcohol) is the generation of oxidative stress, since insufficient or inappropriate consumption of folic acid, which has an antioxidant action, may facilitate teratogenesis by these factors.

Vitamin A intake

The teratogenic effect of retinoic acid —a vitamin A derivative— on cardiovascular morphogenesis has been demonstrated in animal models at both higher[38,39] and lower than normal doses.[40,41] In this study, 6.66% of the mothers took a multivitamin and were unaware of its vitamin A content, and even 3.33% claimed to have specifically consumed vitamin A. In this regard, there is a need to raise awareness of the risk of excessive supplementation and the need to discuss micronutrient intake with the physician.

Use of warfarin

Exposure to warfarin between the 6th and 9th week of pregnancy results in hypoplasia of the nasal bone; depressed nasal bridge; deep depression between the nose wings and nasal tip; punctate calcifications of the epiphysis of the axial skeleton, proximal femur, and calcaneus bone (which disappear after the first year); hypoplastic distal phalanges that look like inverted triangles; low birth weight; and sometimes CHD. Moreover, exposure between the 14th and 20th week produces microcephaly, hydrocephaly, Dandy-Walker malformation, agenesis of the corpus callosum, cerebellar degeneration, seizures, spasticity, intellectual disability, language disorders, optic atrophy, cataracts, microphthalmia, Peters anomaly, intrauterine growth restriction and scoliosis.[8]

This study found a mother exposed to warfarin since the 9th week; her child presented with non-syndromic transposition of the great arteries and none of the other characteristics of fetal warfarin syndrome. Thus, it is evident that there is a need to educate medical personnel about drug teratogenesis and pharmacological alternatives in order to obtain therapeutic effects with drugs without teratogenic potential.

Use of misoprostol

Prenatal exposure to misoprostol in the first trimester of pregnancy for abortion purposes has been associated with Moebius sequence, limb defects, among other congenital anomalies.[42] For example, Pachajoa *et al.*[43] reported a case of prenatal exposure to misoprostol in which the newborn presented CHD.

This study found a mother exposed to this drug in the second month of pregnancy, with a child that had subvalvular aortic stenosis, tricuspid but functionally bicuspid aortic valve and aortic vascular ring in the descending thoracic aorta.

The limitations of this research include that the sample used was small and the methodology employed has risk of memory bias. In addition, exposures were evaluated only through questions to the patients' mothers and reviews of available medical history at the time of evaluation, while no laboratory exams were performed to determine exposures.

Conclusions

This case series presents several prenatal exposures associated with potential risk for CHD, such as maternal diabetes, vitamin A intake, undergoing unprotected x-ray studies, altered pregestational BMI, alcohol consumption, passive smoking and inadequate folic acid supplementation.

Insufficient or untimely intake of folic acid could facilitate the generation of teratogenic effects of oxidizing substances. Therefore, women in Cali should be educated about the importance of adequate folic acid intake and the risks of exposure to teratogenic agents during pregnancy.

Prenatal detection of congenital defects, including heart disease, was low (10%), which highlights the need to implement neonatal CHD screening with pulse oximetry.

Conflicts of interest

None stated by the authors.

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