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ORIGINAL RESEARCH

Prevalence of congenital anomalies and factors associated with their development at a national referral hospital in Quito, Ecuador

Prevalencia de anomalías congénitas y factores asociados con su desarrollo en un hospital de referencia nacional en Quito, Ecuador

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Abstract

Introduction: Congenital anomalies (CA) have a significant impact on health and quality of life. Therefore, knowing their prevalence and the factors associated with their development is essential for designing and implementing educational and preventive programs.
Objectives: To determine the prevalence of CAs in a national referral hospital in Ecuador between 2009 and 2022 and to explore the factors associated with their development.
Materials and methods: Cross-sectional study conducted using 2 data sets for the period 2009 and 2022: 105 385 live births delivered at the HGOIA (estimation of prevalence) and 26 236 neonates hospitalized in the hospital's neonatology service (exploration of factors associated with the presence of CA). The Chi-square test was used to evaluate differences between groups (neonates with and without congenital defects), and binary logistic regression models, both simple (crude Odds ratio [OR]) and multiple (adjusted OR), were utilized to assess associations between the perinatal conditions considered and the presentation of CAs (overall and per anomaly category).
Results: The prevalence of CA was 2.92% (n=3 075). Anomalies of the nervous system (25.6%), cardiovascular and respiratory systems (21.1%), and musculoskeletal (16.1%) were the most frequent CAs. Maternal age >35 years (OR: 1.20, 95%CI: 1.07-1.33) was positively associated with the presentation of CAs, whereas planned pregnancy (OR: 0.88, 95%CI: 0.81-0.96) and multiple pregnancy (OR: 0.50, 95%CI: 0.42-0.60) were negatively associated. Folic acid supplementation, being male, and several maternal-related factors, among other variables, showed an association with the presence of specific types of CA.
Conclusions: The prevalence of CAs at the HGOIA between 2009 and 2022 is slightly higher than what has been reported in the region, with neurological, cardiovascular and respiratory system anomalies being the most frequent. A positive association was found between maternal age >35 years and the occurrence of CAs, whereas planned pregnancy and multiple pregnancy showed negative associations.

Resumen

Introducción. Las anomalías congénitas (AC) tienen un impacto significativo en la salud y la calidad de vida. Por tanto, conocer su prevalencia y los factores asociados a su desarrollo es esencial para diseñar e implementar programas educativos y preventivos.
Objetivos: Determinar la prevalencia de AC en un hospital de referencia nacional de Ecuador entre 2009 y 2022 y explorar los factores asociados a su presencia.
Materiales y métodos. Estudio transversal realizado con 2 conjuntos de datos para el periodo 2009 y 2022: 105 385 nacidos vivos dados a luz en el HGOIA (estimación de la prevalencia) y 26 236 neonatos hospitalizados en el servicio de neonatología del hospital (exploración de factores asociados a la presencia de AC). Se usó la prueba de Chi cuadrado para evaluar diferencias entre grupos (recién nacidos con y sin defectos congénitos). Además, se usaron modelos de regresión logística binaria, tanto simple (Odds ratio [OR] brutos) como múltiple (OR ajustados) para evaluar las asociaciones entre las condiciones perinatales consideradas y la presencia de AC (en general y por categoría de anomalía).
Resultados. La prevalencia de AC fue 2.92% (n=3 075). Las anomalías del sistema nervioso (25.6%), de los sistemas cardiovascular y respiratorio (21.1%) y musculoesqueléticas (16.1%) fueron las AC más frecuentes. La edad materna >35 años (OR: 1.20, IC95%: 1.07-1.33) se asoció positivamente con la presencia de AC, mientras que el embarazo planificado (OR: 0.88, IC95%: 0.81-0.96) y el embarazo múltiple (OR: 0.50, IC95%: 0.42-0.60) se asociaron negativamente. El consumo de ácido fólico, ser varón y varios factores relacionados con la madre, entre otras variables, mostraron una asociación con la presencia de tipos específicos de AC.
Conclusiones. La prevalencia de AC en el HGOIA entre 2009 y 2022 es ligeramente superior a la reportada en la región, siendo las anomalías del sistema nervioso y las de los sistemas cardiovascular y respiratorio las más frecuentes. Se encontró una asociación positiva entre la edad materna >35 años y la presencia de AC, mientras que la planificación del embarazo y los embarazos múltiples mostraron asociaciones negativas.

Introduction

Congenital anomalies (CA) refers to structural changes that are present at birth and can affect almost any part of the body.[1,2] These birth defects can be detected during gestation, at birth, or later in life and, depending on their severity, can substantially impact mortality and morbidity.

Since CAs may contribute to long-term disability, their development, in addition to causing serious emotional and economic repercussions for the families of the affected children, poses a significant economic burden for health systems and society,[3] with a notable impact on public health.

Major CAs are structural alterations with considerable medical, social, or aesthetic implications that usually require medical or surgical intervention.[4] In this regard, families of children with these defects face significant social and economic burdens that often result in financial ruin due to the high costs of medical care.[5]

Worldwide, the average prevalence of CAs between 1970 and 2017 was 8 224 cases per 1 000 live births, with a consistent increase over time (4 547/1 000 live births in 1970-1974 vs. 9 410/1 000 live births in 2010-2017).[6] It has also been reported that these disorders cause 240 000 neonatal deaths every year and an additional 170 000 deaths in children aged 1 month to 5 years. Moreover, 90% of children born with severe CAs live in low- and middle-income countries.

These anomalies can occur as isolated defects or as part of a pattern of multiple CAs. While syndromic birth defects are referred to as the development of multiple CAs in specific patterns or combinations and with a common underlying cause (about 10-20% of cases), most of these anomalies are not syndromic (i.e., CAs that occur in isolation) and their cause is unknown, so the term "multifactorial" is often used to indicate that their etiology is the product of a combination of various genetic and/or environmental factors.[7]

Due to the limited options for prenatal intervention and the irreversibility of many CAs during fetal development, primary prevention through preconception care is critical.[1-4] It should be noted that the risk of a CA is the same for everyone, regardless of socioeconomic status, race, ethnicity, or other demographic characteristics.[4] However, the risk for specific birth defects varies depending on underlying genetic and/or environmental factors, which are usually investigated using epidemiological data on these anomalies,[4] thus making epidemiological studies in this context highly relevant.[8,9]

In 2010, the 63rd World Health Assembly urged countries to strengthen prevention and awareness of CAs, focusing on the need to understand their causes in order to improve prevention, diagnosis, and treatment.[10] In 2015, the World Health Organization, the Centers for Disease Control and Prevention, and the International Clearinghouse for Birth Defects Surveillance and Research[4] published a manual for the development, implementation, and ongoing improvement of a CA surveillance program. This program is aimed at ensuring that, in all countries, the impact of CAs on morbidity are fully understood, risk variables are evaluated, neonates with such defects are promptly referred to appropriate services, and prevalence statistics are utilized to develop preventative and care initiatives. Similarly, the information gathered through this program is essential to guide the design and implementation of policies aimed at reducing CA cases.[4]

According to Durán *et al.*,[11] in 2019 only 11 Latin American countries (Argentina, Colombia, Costa Rica, Cuba, Dominican Republic, Guatemala, Mexico, Panama, Paraguay, Uruguay, and Venezuela) had CA surveillance systems and said systems were heterogeneous. According to the manual for CA program managers mentioned above, it is

recommended to use the International Classification of Diseases (ICD-10) to report these events to facilitate comparisons between countries.[4] Although Ecuador does not have a national CA surveillance system, the Hospital Gineco-obstétrico Isidro Ayora (HGOIA), located in Quito, uses the *Sistema Informático Perinatal* – SIP (Perinatal Information System), developed by the Centro Latinoamericano de Perinatología, to record data on hospitalized mothers and newborns, including CAs.[12]

In view of the above, the objectives of the present study were to determine the prevalence of CAs in a referral hospital in Ecuador between 2009 and 2022 and to explore the factors associated with their development.

Materials and methods

Study type and data analyzed

Cross-sectional study conducted using two data sets. First, to determine the prevalence of CAs, all live births delivered between January 2009 and December 2022 at the HGOIA (N=105 385), a national referral hospital (tertiary level of care) located in Quito, were considered. Second, in order to explore the factors associated with the presence of CAs, only newborns hospitalized in the neonatology service of the HGOIA in the same period were considered (N=26 552); for this second data set, neonates with incomplete data were excluded, resulting in a sample of 26 236 newborns. Information was obtained from the hospital's SIP.

Variables

Based on the review of the HGOIA's SIP database, data on the following variables were extracted for each newborn hospitalized in the neonatology service and included in the study: maternal age, mother's ethnic self-identification, marital status (having a stable partner), history of miscarriage(s), previous gestations (# deliveries or parity + # miscarriages; the pregnancy of the newborn included in the study was not considered), history of infertility, planned pregnancy, history of type 1 or type 2 diabetes *mellitus* (DM) in the mother, family history of diabetes, folic acid supplementation during pregnancy, alcohol consumption during pregnancy, use of psychoactive substances during pregnancy, exposure to tobacco smoke during pregnancy, presence of gestational diabetes (GDM), sex of the newborn, multiple pregnancy, and presence of and type of CA (the equivalent of the ICD-10 code in the SIP[12] system was used to classify CAs).[13] It should be noted that variables related to maternal weight and infections acquired during gestation were not included due to underreporting.

CAs were classified based on the following categories: anomalies of the nervous system, anomalies of the cardiovascular and respiratory systems, musculoskeletal anomalies, gastrointestinal anomalies, urogenital anomalies, chromosomal anomalies, anomalies of the lip and/or palate, integumentary system anomalies, and other anomalies.

Statistical analysis

The data collected were entered and organized in a database created in Microsoft Excel and subsequently analyzed using the R programming language (version 4.3.0), "Rcmdr" and "EZR" packages.[14] Data are described using absolute and relative frequencies for

categorical variables. For analysis purposes, continuous variables were recoded into nominal or interval categorical variables. The prevalence of CAs was calculated by dividing the number of CA cases by the total number of live births during the study period and is expressed as a percentage.

Regarding inferential statistics, a bivariate analysis (Chi-Square test) was performed to evaluate differences in the variables considered between groups (newborns with and without CAs). Moreover, binary logistic regression models, both simple (raw *Odds ratio* [OR]) and multiple (adjusted OR), were used to evaluate the associations between perinatal conditions (maternal age >35 years, belonging to a minority ethnicity [indigenous, Afro-descendant, others], not having a stable partner, having a history of pregnancy [excluding the pregnancy of the child included in the study], having a history of miscarriage(s), history of infertility, mother with DM, family history of DM, planned pregnancy, folic acid supplementation during pregnancy, alcohol consumption during pregnancy, exposure to tobacco smoke during pregnancy, use of psychoactive substances during pregnancy, presence of GDM, multiple pregnancy, male newborn, and the presence of CA (overall and per anomaly category).

The variables included in the final regression model for each type of anomaly were selected using the following process: 1) selection of variables with the lowest Akaike information criterion value in the simple model, 2) selection of variables with minimum deviance and a statistical significance value of $p<0.05$, and 3) comparison of the full and reduced models using the likelihood ratio test. This process optimized model fit and accuracy by minimizing the inclusion of non-relevant variables. The models that showed a good fit to the observed data according to the Hosmer-Lemeshow test ($p>0.05$) are presented below.

A statistical significance level of $p<0.05$ was considered in all statistical analyses.

Ethical considerations

The study followed the ethical principles for biomedical research involving human subjects established in the Declaration of Helsinki.[15] In addition, it was approved by the Ethics Committee for Research involving Human Subjects of the Universidad Central del Ecuador (CEICH-UCE) as stated in Minutes 009-DOC-FCM-2023 of September 7, 2023. Since an anonymized database was used, no informed consent was required.

Results

A total of 3 075 out of 105 385 live births during the study period at HGIOA had CAs, representing a prevalence of 2.92% (95%CI: 2.82-3.02). Of these, 2 136 (69.46%, 95%CI: 67.8-71.1) had major birth defects, accounting for 2.03% (95%CI: 1.95-2.11) of the total births. In this context, anomalies of the nervous system (n=788, 25.63%; 95%CI: 24.07-27.17), cardiovascular and respiratory system (n=654, 21.27%; 95%CI: 19.82-22.72), and musculoskeletal system (n=494, 16.06%; 95%CI: 14.77-17.37) were the most frequent CAs (Table 1).

Table 1. Distribution of congenital anomalies reported in newborns admitted to the neonatology service of the Hospital Gineco-Obstétrico Isidro Ayora between 2009 and 2022 according to the established categories (n=3 075).

SIP[12] code	ICD-10[13] code	Type of congenital anomaly	(n)	(%)
	Q00-Q07	**Nervous system**	**788**	**25.63%** (95%CI: 24.07-27.17)
123	Q03	Congenital hydrocephalus	322	40.86%
121	Q05	Spina bifida	118	14.97%
124	Q02	Microcephaly	63	7.99%
122	Q04.3	Other reduction deformities of brain	32	4.06%
120	Q00.0	Anencephaly	19	2.41%
125	Q04.2	Holoprosencephaly	15	1.90%
126	Q07	Other congenital malformations of the nervous system	219	27.79%
	Q20-Q28 and Q30-Q34	**Cardiovascular and respiratory system**	**654**	**21.27%** (95%CI: 19.82-22.72)
134	Q22.0	Pulmonary valve atresia	8	1.22%
135	Q22.4	Congenital tricuspid stenosis	6	0.91%
133	Q21.1	Atrial septal defect	4	0.61%
137	Q25.1	Coarctation of the aorta	13	1.98%
138	Q26.2	Total anomalous pulmonary venous connection	2	0.30%
136	Q22.6	Hypoplastic right heart syndrome	5	0.76%
130	Q21.3	Tetralogy of Fallot	8	1.22%
129	Q20.1/Q20.2	Congenital malformations of cardiac chambers and connections	7	1.07%
128	Q20.0	Common arterial trunk	3	0.45%
131	Q20.4	Double inlet ventricle	8	1.22%
139	Q28/Q30-Q34	Congenital malformations of the respiratory system	590	90.21%
	Q65-Q79	**Musculoskeletal**	**494**	**16.06%** (95%CI: 14.77-17.37)
146	Q79.3	Gastroschisis	183	37.04%
145	Q79.2	Omphalocele	40	8.09%
163	Q77/Q78	Osteochondrodysplasia	27	5.46%
165	Q79.0	Congenital diaphragmatic hernia	42	8.50%
164	Q66	Congenital deformities of the feet	54	10.93%
161	Q69	Polydactyly	38	7.69%
162	Q70	Syndactyly	10	2.02%
168	Q68	Other congenital musculoskeletal deformities	100	20.24%
	Q39-Q45	**Gastrointestinal**	**177**	**5.76%** (95%CI: 4.94-6.58)
147	Q41.0	Congenital absence, atresia, or stenosis of the duodenum	47	25.55%
142	Q39.0	Esophageal atresia without a fistula	39	22.03%
144	Q42.2	Congenital absence, atresia, and stenosis of the anus with a fistula	30	16.94%
148	Q41.1	Congenital absence, atresia, and stenosis of the jejunum	16	90.3%
141	Q39.2	Congenital trachea-esophageal fistula without atresia	15	8.47%

SIP[12] code	ICD-10[13] code	Type of congenital anomaly	(n)	(%)
149	Q41.2	Congenital absence, atresia, and stenosis of the ileum	5	2.82%
143	Q42	Congenital absence, atresia and stenosis of large intestine	3	1.69%
150	Q45	Other congenital malformations of the digestive system	22	12.42%
	Q60-Q64 and Q50-Q56	**Renal pelvis and ureter**	**327**	**10.63%** (95%CI: 9.53-11.73)
154	Q62.0	Congenital hydronephrosis	81	24.77%
153	Q61.3	Polycystic kidney, unspecified	46	14.06%
152	Q60.1	Renal agenesis, bilateral	8	2.44%
156	Q63/Q64	Other congenital malformations of kidney	71	21.71%
151	Q50-Q56	Congenital malformations of genital organs	121	37.00%
	Q90-Q99	**Chromosomal**	**252**	**8.19%** (95%CI: 7.23-9.15)
159	Q90	Down syndrome	208	82.54%
158	Q91	Trisomy 18	14	5.55%
157	Q91	Trisomy 13	5	1.98%
160	Q92-Q99	Other chromosome abnormalities	25	9.92%
	Q35-Q37	**Lip and/or palate**	**223**	**7.25%** (95%CI: 6.33-8.17)
126	Q36	Cleft lip	32	14.34%
140	Q35	Cleft palate	26	11.65%
	Q37	Cleft palate with cleft lip	165	73.99%
	Q80-Q89	**Skin and integument**	**147**	**4.78%** (95%CI: 4.04-5.52)
169	Q80-Q89	Other congenital malformations	147	100%
		Other anomalies	**13**	**0.42%** (95%CI: 0.18-0.66)
166	P83.2 *	Hydrops fetalis	11	84.61%
167	P01.2 *	Newborn affected by oligohydramnios	2	15.39%

* These anomalies are not included in the ICD-10 within the chapter on congenital defects, so their SIP code was used instead.

Group comparison

In the bivariate analysis (Table 2), statistically significant differences were found between groups (neonates with CAs vs. neonates without CAs) in the following variables: maternal age (p=0.003), previous pregnancies (p=0.007), planned pregnancy (p=0.003), and multiple pregnancy (p<0.001).

Table 2. Comparison of variables between groups (newborns with and without congenital anomalies).

Variable	Category	Congenital defects		No congenital defects		*p*-value (X^2)
		(n)	(%)	(n)	(%)	
Maternal age	<20 years	814	12.1%	5 886	87.9%	0.003
	20-29 years	1 390	11.4%	10 785	88.6%	
	30-39 years	725	11.3%	5 668	88.7%	
	≥40 years	146	15.1%	822	84.9%	
Ethnicity	Mestizo	2 902	11.8%	21 657	88.2%	0.21
	Indigenous	63	11.5%	487	88.5%	
	Afro-descendant	56	10.8%	463	89.2%	
	White	15	7.6%	183	92.4%	
	Other	39	9.5%	371	90.5%	
Stable partner	Yes	2 271	11.7%	6045	88.3%	0.96
	No	804	11.7%	17 116	88.3%	
Previous pregnancies	None	1 259	12.3%	9 000	87.7%	0.007
	1 to 3	1 504	11.1%	12 016	88.9%	
	4 or more	312	12.7%	2 145	87.3%	
History of miscarriage(s)	Yes	752	11.6%	5 734	88.4%	0.72
	No	2 323	11.8%	17 427	88.2%	
History of infertility	Yes	44	13.9%	273	86.1%	0.26
	No	3 031	11.7%	22 888	88.3%	
Presence of diabetes mellitus in the mother	Yes	71	12.4%	502	87.6%	0.59
	No	3 004	11.7%	22 659	88.3%	
Family history of diabetes	Yes	659	11.3%	5 166	88.7%	0.27
	No	2 416	11.8%	17 995	88.2%	
Planned pregnancy	Yes	917	10.9%	7 516	89.1%	0.003
	No	2 158	12.1%	15 645	87.9%	
Folic acid supplementation during pregnancy	Yes	2 459	11.7%	18 544	88.3%	0.91
	No	616	11.8%	4 617	88.2%	
Alcohol consumption during pregnancy	Yes	101	13.8%	633	86.2%	0.09
	No	2 974	11.7%	22 528	88.3%	
Exposure to tobacco smoke during pregnancy	Yes	162	10.2%	1 425	89.8%	0.05
	No	2 913	11.8%	21 736	88.2%	
Use of psychoactive substances during pregnancy	Yes	13	8.5%	140	91.5%	0.26
	No	3062	11.7%	23 021	88.3%	
Gestational diabetes	Yes	65	11.6%	494	11.7%	0.99
	No	3 010	84.6%	22 667	88.3%	
Multiple pregnancy	Yes	137	6.5%	1 955	93.5%	<0.001
	No	2 938	12.2%	21 206	87.8%	
Male newborn	Yes	1 696	12%	12 481	88%	0.19
	No	1 379	11.4%	10 680	88.6%	

Overall factors associated with the presence of CAs

In the univariate analysis, a positive association was observed between maternal age >35 years and the presence of a CA (OR: 1.19, 95%CI: 1.07-1.32; p=0.001). In contrast, a negative association was found between the development of congenital defects and multiple pregnancy (OR: 0.50, 95%CI: 0.42;0.60; p<0.001) and planned pregnancy (OR: 0.88, 95%CI: 0.81-0.96; p=0.003) (Table 3).

Table 3. Association of variables with congenital anomalies. Simple binary logistic regression model.

Variable	OR (95%CI)	*p*-value
Maternal age >35 years	1.19 (1.07-1.32)	0.001
Minority ethnic groups	0.85 (0.72-1.01)	0.06
No stable partner	0.99 (0.91-1.09)	0.95
History of pregnancy (excluding the pregnancy of the child included in the study)	0.97 (0.91-1.03)	0.32
History of miscarriage(s)	0.98 (90-1.07)	0.71
History of infertility	0.95 (0.76-1.21)	0.72
Mother with diabetes mellitus	1.07 (0.83-1.37)	0.61
Family history of diabetes	0.95 (0.86-1.04)	0.27
Planned pregnancy	0.88 (0.81-0.96)	**0.003**
Folate supplementation	0.99 (0.90-1.09)	0.89
Alcohol consumption	1.21 (0.97-1.50)	0.08
Exposure to tobacco smoke	0.84 (0.71-1)	0.053
Psychoactive substance use	0.69 (0.39-1.23)	0.21
Mother with gestational diabetes	0.99 (0.76-1.29)	0.94
Product of multiple pregnancy	0.50 (0.42-0.60)	**<0.001**
Male newborn	1.05 (0.97-1.14)	0.18

OR: Odds ratio, CI: 95% confidence interval.

Variables with significance in the bivariate analysis or with theoretical relevance were selected for multivariate analysis. The analysis mentioned above supported the finding that maternal age >35 years is positively associated with the development of a CA (OR: 1.20, 95%CI: 1.07-1.33; p=0.001). Likewise, it was confirmed that planned pregnancy (OR: 0.88, 95%CI: 0.81-0.96; p=0.004) and multiple pregnancy (OR: 0.50, 95%CI: 0.42-0.60; p<0.001) were negatively associated with the occurrence of a CA (Table 4).

Table 4. Factors associated with congenital anomalies. Multiple binary logistic regression model.

Variable	Adjusted OR (95%CI)	*p*-value
Maternal age >35	1.20 (1.07-1.33)	0.001
Planned pregnancy	0.88 (0.81;0.96)	0.004
Product of multiple pregnancy	0.50 (0.42;0.60)	<0.001

Factors associated with the presence of CAs per type

The univariate analysis showed that:

i. Maternal age >35 years was positively associated with the presence of chromosomal anomalies (OR: 5.32, 95%CI: 4.04-6.99; p<0.001) and negatively associated with the presence of nervous system (OR: 0.75, 95%CI: 0.59-0.96; p=0.02), musculoskeletal (OR: 0.64, 95%CI: 0.47-0.88; p=0.005), and lip and palate (OR: 0.61, 95%CI: 0.39-0.97; p=0.03) anomalies.
ii. Having a history of pregnancy was positively associated with the presence of chromosomal anomalies (OR: 2.17, 95%CI: 1.78-2.64; p<0.001) and negatively associated with the presence of nervous system (OR: 0.86, 95%CI: 0.76-0.98; p=0.02) and musculoskeletal (OR: 0.79, 95%CI: 0.67-0.92; p=0.003) anomalies.
iii. Having a history of miscarriage(s) was positively associated with the presence of chromosomal (OR: 1.85, 95%CI: 1.41-2.43; p<0.001) and cardiovascular and respiratory system anomalies (OR: 1.29, 95%CI: 1.06-1.57; p=0.01) and negatively associated with the presence of gastrointestinal anomalies (OR: 0.66, 95%CI: 0.45-0.98; p=0.04).
iv. Having a history of infertility was negatively associated with the presence of nervous system anomalies (OR: 0.54, 95%CI: 0.29-1; p= 0.04).
v. The presence of DM in the mother was positively associated with the development of cardiovascular and respiratory system anomalies (OR: 2.79, 95%CI: 1.73-4.51; p<0.001).
vi. Supplementation with folic acid during pregnancy was positively associated with the presence of urogenital (OR: 1.52, 95%CI: 1.08-2.14; p=0.01) and integumentary anomalies (OR: 1.84, 95%CI: 1.11-3.04; p=0.01) and negatively associated with the presence of nervous system anomalies (OR: 0.79, 95%CI: 0.65-0.96; p=0.02).
vii. The presence of GDM was positively associated with the development of cardiovascular and respiratory system anomalies (OR: 2.21, 95%CI: 1.33-3.69; p=0.002).
viii. Being male was positively associated with the presence of urogenital anomalies (OR: 2.32, 95%CI: 1.76-3.04; p<0.001) and negatively associated with the presence of musculoskeletal anomalies (OR: 0.81, 95%CI: 0.66-0.99; p=0.03).

Associations between the perinatal variables considered and the development of a CA per type are presented in Table 5.

Table 5. Association between the variables considered and the development of congenital anomalies per anomaly type. Simple binary logistic regression model.

Variables	Nervous system		Cardiovascular and respiratory systems		Musculoskeletal		Chromosomal		Lip and palate		Gastrointestinal		Urogenital		Integumentary	
	OR (95%CI)	*p*-value	OR (95%CI)	*p*-value	OR (95%CI)	*p*-value	OR (95%CI)	*p*-value	OR (95%CI)	*p*-value	OR (95%CI)	*p*-value	OR (95%CI)	*p*-value	OR (95%CI)	*p*-value
Maternal age >35 years	0.75 (0.59-0.96)	**0.02**	0.86 (0.67-1.12)	0.26	0.64 (0.47-0.88)	0.005	5.32 (4.04-6.99)	**<0.001**	0.61 (0.39-0.97)	0.03	1.00 (0.65-1.54)	0.93	0.90 (0.63-1.29)	0.57	0.96 (0.60-1.55)	0.89
Minority ethnic groups	0.92 (0.64-1.32)	0.67	0.97 (0.66-1.42)	0.87	1.08 (0.71-1.64)	0.7	0.98 (0.56-1.73)	0.96	1.04 (0.58-1.86)	0.89	0.67 (0.31-1.47)	0.32	1.32 (0.81-2.14)	0.25	1.10 (0.55-2.20)	0.78
No stable partner	1.22 (1.02-1.46)	**0.02**	1.12 (0.92-1.36)	0.26	0.82 (0.65-1.04)	0.11	0.50 (0.36-0.72)	**<0.001**	1.02 (0.74-1.39)	0.9	1.41 (0.96-2.05)	0.72	1.14 (0.86-1.50)	0.34	1.31 (0.91-1.87)	0.14
Previous pregnancies	0.86 (0.76-0.98)	**0.02**	1.13 (0.98-1.29)	0.07	0.79 (0.67-0.92)	**0.003**	2.17 (1.78-2.64)	**<0.001**	0.95 (0.76-1.18)	0.64	1.09 (0.79-1.49)	0.58	0.89 (0.74-1.09)	0.26	0.89 (0.64-1.25)	0.51
History of miscarriage(s)	0.83 (0.68-1.01)	**0.05**	1.29 (1.06-1.57)	**0.01**	0.89 (0.70-1.13)	0.33	1.85 (1.41-2.43)	**<0.001**	0.83 (0.60-1.16)	0.29	0.66 (0.45-0.98)	0.04	0.92 (0.69-1.23)	0.58	0.65 (0.42-1)	0.05
History of infertility	0.54 (0.29-1)	**0.04**	1.43 (0.63-3.23)	0.38	1.40 (0.55-3.58)	0.47	1.22 (0.37-3.90)	0.73	0.77 (0.27-2.20)	0.63	1.29 (0.30-5.36)	0.72	0.78 (0.30-2.00)	0.6	infinite	0.97
Presence of diabetes in the mother	0.52 (0.27-1)	**0.05**	2.79 (1.73-4.51)	**<0.001**	0.50 (0.021-1.18)	0.11	1.23 (0.55-2.72)	0.6	1.19 (0.50-2.77)	0.69	0.71 (0.22-2.30)	0.57	1.09 (0.49-2.44)	0.83	0.28 (0.03-2.30)	0.2
Family history of diabetes	1.10 (0.90-1.33)	0.35	1.07 (0.86-1.32)	0.53	0.95 (0.74-1.22)	0.7	0.75 (0.54-1.06)	0.11	1.22 (0.88-1.67)	0.22	0.73 (0.49-1.10)	0.13	0.90 (0.66-1.23)	0.52	0.93 (0.62-1.41)	0.7
Planned pregnancy	0.86 (0.72-1.03)	0.1	1.10 (0.90-1.32)	0.33	1.08 (0.87-1.34)	0.46	0.75 (0.55-1.01)	**0.05**	0.94 (0.69-1.27)	0.7	1.31 (0.67-2.53)	0.42	1.14 (0.87-1.48)	0.32	1.04 (0.72-1.49)	0.83
Folate supplementation	0.79 (0.65-0.96)	**0.02**	0.94 (0.76-1.17)	0.58	1.20 (0.80-1.31)	0.84	0.88 (0.65-1.21)	0.45	1.24 (0.86-1.78)	0.24	0.85 (0.59-1.22)	0.38	1.52 (1.08-2.14)	0.01	1.84 (1.11-3.04)	0.01
Alcohol consumption	0.75 (0.46-1.23)	0.25	0.79 (0.47-1.34)	0.39	1.58 (0.97-2.57)	0.06	1.10 (0.54-2.21)	0.79	1.10 (0.52-2.30)	0.65	0.84 (0.34-2.11)	0.72	0.73 (0.33-1.60)	0.43	1.75 (0.83-3.68)	0.13
Exposure to tobacco smoke	0.70 (0.47-1.04)	0.08	1.10 (0.75-1.61)	0.61	1.40 (0.94-2.09)	0.09	0.89 (0.48-1.63)	0.7	1.12 (0.62-1.01)	0.69	0.50 (0.20-1.25)	0.14	1.34 (0.81-2.21)	0.24	1.04 (0.49-2.15)	0.92
Use of psychoactive substances	0.52 (0.11-2.38)	0.4	0.30 (0.04-2.37)	0.25	1.02 (0.22-4.60)	0.98	infinite	0.97	2.34 (0.51-10.60)	0.27	1.37 (0.17-10.60)	0.76	1.81 (0.40-8.22)	0.44	infinite	0.97
Gestational diabetes	0.58 (0.30-1.13)	0.1	2.21 (1.33-3.69)	**0.002**	0.89 (0.44-1.82)	0.76	1.36 (0.61-3.02)	0.44	0.83 (0.30-2.32)	0.73	0.78 (0.24-2.54)	0.69	0.82 (0.32-2.07)	0.74	0.30 (0.04-2.22)	0.24
Product of multiple pregnancy	0.91 (0.61-1.37)	0.67	1.23 (0.82-1.84)	0.3	1.07 (0.67-1.71)	0.77	0.41 (0.16-1.02)	**0.05**	1.24 (0.67-2.28)	0.48	1.31 (0.67-2.53)	0.42	0.95 (0.52-1.75)	0.87	1.25 (0.59-2.60)	0.55
Male newborn	0.89 (0.76-1.05)	1.7	1.40 (0.87-1.23)	0.69	0.81 (0.66-0.99)	**0.03**	0.78 (0.60-1.02)	0.06	1.15 (0.87-1.52)	0.32	0.85 (0.63-1.16)	0.3	2.32 (1.76-3.04)	<0.001	1.19 (0.85-1.67)	0.31

OR: Odds ratio; CI: 95% confidence interval.

The multiple binary logistic regression model (multivariate analysis) (Table 6), in which the associations between variables were adjusted by simultaneously controlling for multiple factors, showed that:

i. Maternal age >35 years was associated with a higher probability of chromosomal anomalies (OR: 4.58, 95%CI: 3.39-6.17; p<0.001) and a lower probability of musculoskeletal anomalies (OR: 0.69, 0.50-0.96; p=0.03).
ii. Folic acid supplementation during pregnancy was associated with a lower probability of nervous system anomalies (OR: 0.79, 95%CI: 0.65-0.97; p=0.02) and with a higher probability of urogenital anomalies (OR: 1.47, 95%CI: 1.04-2.08; p=0.02).
iii. Having a history of miscarriage was associated with a higher probability of cardiovascular and respiratory anomalies (OR: 1.27, 95%CI: 1.04-1.54; p=0.01).
iv. The presence of DM in the mother was associated with a higher probability of cardiovascular and respiratory anomalies (OR: 2.50, 95%CI: 1.30-4.78; p=0.005).
v. Being male was associated with a higher probability of urogenital anomalies (OR: 2.30, 95%CI: 1.75-3.02; p<0.001) and with a lower probability of musculoskeletal anomalies (OR: 0.82, 95%CI: 0.67-0.99; p=0.04).

Table 6. Factors associated with the development of congenital anomalies per type of anomaly. Multiple binary logistic regression model.

Type of congenital anomaly	Variables	Adjusted OR (95%CI)	*p*-value
Nervous system	Maternal age >35 years	0.80 (0.41-1.49)	0.1
	No stable partner	1.13 (0.93-1.37)	0.2
	Previous pregnancies	0.88 (0.74-1.06)	0.19
	History of infertility	0.55 (0.29-1.02)	0.05
	Folate supplementation	0.79 (0.65-0.97)	0.02
Cardiovascular and respiratory system	Previous miscarriages	1.27 (1.04-1.54)	0.01
	Presence of diabetes mellitus in the mother	2.50 (1.30-4.78)	0.005
	Presence of gestational diabetes	1.15 (0.56-2.32)	0.7
Musculoskeletal	Maternal age >35 years	0.69 (0.50-0.96)	0.03
	Previous pregnancies	0.84 (0.68-1.03)	0.1
	Male newborn	0.82 (0.67-0.99)	0.04
Chromosomal	Maternal age >35 years	4.58 (3.39-6.17)	<0.001
	No stable partner	0.78 (0.53-1.14)	0.19
	Previous pregnancies	1.15 (0.79-1.66)	0.45
	Previous miscarriages	1.34 (0.97-1.82)	0.06
Urogenital	Folate supplementation	1.47 (1.04-2.08)	0.02
	Male newborn	2.30 (1.75-3.02)	<0.001

Discussion

In the present study, the prevalence of CAs among live births delivered at the HGOIA between 2009 and 2022 was 2.91% (n=3 075). This is slightly higher than the 2.1% reported in a study conducted by Palacios-Arenas & Terrones-Saldívar[16] in Aguascalientes, Mexico, using data from 267 489 live births during 2008-2017 and the 1.7% described by Muñoz *et al.*[17] at the Hospital Dr. Hernán Henríquez Aravena in Temuco, Chile (54 241 live newborns between 2009 and 2018). In this regard, it should be noted that the HGOIA is a national referral hospital in Ecuador that serves patients from different regions of the country, which, together with the large study period, could explain the higher prevalence of CAs observed here.

We also found that anomalies of the nervous system (n=788, 25.63%, 95%CI: 24.0-27.2), cardiovascular and respiratory system (n=654, 21.27%, 95%CI: 19.6-22.6), and musculoskeletal (n=494, 16.06%, 95%CI: 14.8-17.4) were the most frequent congenital defects. This finding partially coincides with that reported by Castro-González *et al.*,[18] who, in a study conducted in 1 844 patients with CA treated in a perinatology unit in Caracas, Venezuela, between 2015 and 2020, reported that anomalies of the central nervous system (29.7%), cardiovascular system (23.6%) and genitourinary system (17.5%) were the most common. Furthermore, Avila-Mellizo,[19] in a study that included all officially reported CA cases in Colombia between 2015 and 2017 (n=18 540), reported that anomalies of the musculoskeletal system (21.1-27.8%), circulatory system (14.6-23.0), and nervous system (9.7-20.2%) were the most frequent

Similarly, Zahed-Pasha *et al.*[20] established in a systematic review that the most common malformations in Iran are orofacial clefts (1.4 per 1 000 births), neural tube defects (3.2 per 1 000 births), urogenital anomalies (3.9 per 1 000 births), musculoskeletal anomalies (3.3 per 1 000 births), and cardiovascular anomalies (3.3 per 1 000 births).

It is worth mentioning that in our study cardiovascular and respiratory congenital anomalies were grouped in the same category following the ICD-10 classification due to the coding system used in the SIP.

Factors associated with the presence of congenital anomalies in general

In the present study, maternal age >35 years was positively associated with the presence of a CA (OR: 1.20, 95%CI: 1.07-1.33; p=0.001). This finding is in line with the literature, as several studies report that children of older mothers (>35 years) have a higher probability of developing a CA.[21-23] Furthermore, both planned pregnancy (OR: 0.88, 95%CI: 0.81-0.96, p<0.05) and multiple pregnancy (OR: 0.50, 95%CI: 0.42-0.60, p<0.05) had negative associations.

Although none of the other variables analyzed in the present study were associated with the development of a CA, several associations (negative and positive) between these variables and the presence of these defects are reported in the literature.

For example, regarding male sex, the studies conducted by Williford *et al.*[24] with data from 11 379 babies with birth defects born between 1997 and 2011 in 10 U.S. states and by Stallings *et al.*[25] with data on 12 563 163 children born between 2012 and 2016 in the United States with abdominal wall defects report a higher frequency of the male sex. Consequently, it could be assumed that being male may be associated with a higher risk of these defects.

Concerning folic acid supplementation, Abebe *et al.*,[8] in a case-control study (251 newborns with CA and 887 newborns without CA) conducted between May 2016 and May 2018 in 6 hospitals of southwestern Ethiopia, reported that taking folic acid supplements during early pregnancy showed a protective effect against CAs (OR: 0.428, 99%CI: 0.247-0.740). Likewise, Moges *et al.*,[22] in a systematic review and meta-analysis including 32 studies (626 983 participants in total), found that not taking folic acid increases the risk of these anomalies (OR: 2.67, 95%CI: 1.42-5.00).

As for alcohol and psychoactive substance use, both factors were associated with an increased risk of CA (OR: 3.15, 95%CI: 1.4-7.04 and OR: 2.74, 95%CI: 1.29-5.81) in the systematic review by Moges *et al.*[22] With respect to tobacco smoke exposure during pregnancy, Yang *et al.*[26] reported in a study using data from 12 144 972 live births registered between 2016 and 2019 in the U.S. National Vital Statistics System that women who never smoked before and during pregnancy showed a lower risk of CA (RR: 0.77, 95%CI: 0.73-0.81).

Regarding the presence of maternal DM and GDM, Wu *et al.*,[27] in a study using data from 29 211 974 live births registered between 2011 and 2018 in the U.S. National Vital Statistics System, found that both factors were associated with an increased risk of CA (RR: 2.44, 95%CI: 2.33-2.55 and RR: 1.28, 95%CI: 1.24-1.31).

Factors associated with congenital anomalies per type of anomaly

In the present study, folic acid supplementation during pregnancy was negatively associated with the development of CAs of the nervous system (OR: 0.79, 95%CI: 0.65-0.97; p=0.02). This finding is consistent with the literature, as it has been widely described that folic acid supplementation has a protective effect against neural tube defects, the second most frequent CA of the nervous system, especially if the supplementation begins before pregnancy or during the first trimester. This is pointed out by Avagliano *et al.*[28] in a review of systematic reviews and by the U.S. Preventive Services Task Force in its recommendations on the use of folic acid for the prevention of neural tube defects.[29]

A positive association was also observed between the development of cardiovascular and respiratory CAs and the presence of DM in the mother. This finding is consistent with that reported by Postoev *et al.*,[30] who, in a study conducted with data from 4 862 newborns with CA in Murmansk and Arkhangelsk (Russia), found that cardiovascular malformations are a common type of CA in newborns born to mothers with type 1 DM and that women with pregestational DM have a 4.81-fold higher risk of giving birth to a child with this group of malformations. Similarly, Maduro *et al.*,[31] in a literature review, established that the presence of DM in the mother has a negative influence on pregnancy and fetal cardiac development, even in women with adequate glycemic control, with hyperglycemia being the main teratogenic factor due to the production of mitochondrial superoxide radicals.

Furthermore, a positive association was observed between having a history of miscarriage(s) and the development of cardiopulmonary CA. This finding is in agreement with what was reported by Ruan *et al.*[32] in a study of 5 024 pregnant women who underwent fetal echocardiography between May 2018 and September 2019 in a hospital in China, in which a history of miscarriage was positively associated with an increased risk of fetal coronary heart disease (OR: 1.59, 95%CI: 1.33-1.91). Contrary to previous studies,[33-35] the present study showed that maternal age >35 years and male sex were negatively associated with the presence of musculoskeletal anomalies.

In addition, the present study found that folic acid supplementation during pregnancy was positively associated with the presence of urogenital CAs. Unfortunately, there are no studies that allow a comparison of this finding. Furthermore, being male was positively associated with the presence of urogenital CAs. This finding is in line with the study conducted by Núñez-Copo & Frómeta-Montoya[36] in Cuba in 453 fetuses diagnosed by ultrasound with congenital defect of the genitourinary tract between January 2013 and December 2018. They reported that these anomalies were more frequent in males (64.6%), which may be due to fact that congenital cryptorchidism is one of the most common congenital urogenital malformations.[37]

With respect to maternal age >35 years, this factor was significantly associated with the development of several types of CA. In this regard, there was a positive association with the presence of chromosomal anomalies, which is consistent with the findings described in the literature reviews by Harris *et al.*[21] and Mikwar *et al.*,[38] who stated that chromosomal segregation errors during meiotic divisions in advanced maternal age (>35 years) are increasingly

common and lead to the production of oocytes with an incorrect number of chromosomes, a condition known as aneuploidy (the most common type of chromosomal anomaly).

On the other hand, maternal age >35 years was negatively associated with the presence of lip and palate anomalies, a finding that differs from the reports by Heydari *et al.*[39] in a study using data from 22 651 555 live births registered in the U.S. National Center for Health Statistics between January 2016 and December 2021, in which mothers aged 20-24 years had a significantly higher risk of having a child with a cleft lip with or without cleft palate (OR: 1.07, 95%CI: 1.01-1.13). It is important to keep in mind that the development of these anomalies has been associated with some factors such as maternal exposure to pesticides, antibiotic use, parental smoking, threatened miscarriage, use of anticonvulsant, retinoic acid use, folic acid deficiency, class 2 obesity, hypertension, and pregestational DM.[39-41]

We also observed that folic acid supplementation was positively associated with the presence of integumentary anomalies. Unfortunately, we found no primary studies that addressed factors associated with the development of this type of CA, but based on our literature search, the only relatively recent primary study on the subject was conducted by Sarikaya-Solak *et al.*[42] with data from 1 000 newborns treated between October 2011 and April 2012 in a hospital in Turkey, in which they reported a prevalence of integumentary CA of 4.8%; nevertheless, the study is purely descriptive and does not provide information on possible associated factors, which is why further research on the subject is required.

Lastly, although none of the variables considered in the present study were associated with the development of gastrointestinal CA, it is important to note that several protective and risk factors for these anomalies have been described in the literature, depending on their type and location. For example, Wu *et al.*,[43] in a study of 136 children with anorectal malformations treated between December 2018 and December 2019 in a university hospital in Chongqing (China), found that the presence of maternal respiratory infections (aOR: 2.44, 95%CI: 1.29-4.63) and urinary tract infections in the first trimester of pregnancy (aOR: 2.67, 95%CI: 1.11-6.38), the presence of anemia during pregnancy (aOR: 5.69, 95%CI: 1.11-6.38), and maternal exposure to harmful substances 6 months before pregnancy and during the first trimester of pregnancy (aOR: 13.82, 95%CI: 3.86-49.32) were associated with an increased risk of these malformations, while the use of folic acid supplements (aOR: 0.31, 95%CI: 0.14-0.65) and multivitamins (aOR: 0.34, 95%CI: 0.15-0.79) had a protective effect.

The main strengths of the present study include the extensive period studied (+10 years), the detailed classification of the CAs according to the SIP and ICD-10 recommendations, and its sample size, which, in addition to being large, is representative of the country as it comes from a national reference hospital, which allows generalization of the findings. On the other hand, the limitations include possible information biases due to underreporting and coding errors in the SIP records. Similarly, due to its retrospective design, there is a possibility of information bias and residual confounding bias. In addition, although several variables were controlled for, other possible confounding variables may not have been considered.

Conclusion

The present study showed a slightly higher prevalence of CAs in the country compared to what has been reported in the region, with anomalies of the nervous system and the cardiovascular and respiratory systems being most frequent. A positive association was

found between maternal age >35 years and the presence of CAs in general, whereas planned pregnancy and multiple pregnancy showed negative associations. Finally, several associations, both positive and negative, were observed between different factors and specific types of CA, including chromosomal, musculoskeletal, urogenital, cardiovascular and respiratory, and nervous system anomalies.

Conflicts of interest

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