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Original Article

Congenital heart defects in La Réunion Island: a 6-year survey within a EUROCAT-affiliated congenital anomalies registry

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Abstract *Objectives:* This study compares the prevalence and perinatal mortality of congenital heart defects on La Réunion with European (EUROCAT) standards. *Methods and results:* Data were extracted from a EUROCAT-affiliated congenital malformations registry, covering 88,025 births during the period 2002–2007, on the whole island territory. A total of 512 congenital heart defects were registered, including 424 live births, 18 foetal deaths from 16 weeks of gestation, and 70 terminations of pregnancy. The total prevalence of congenital heart defects was 5.8 per 1000 births and live birth prevalence was 4.8 per 1000. The total prevalence of non-chromosomal congenital heart defects was 5.1 per 1000 births, of which 3% were perinatal deaths, 33.3% prenatally diagnosed, and 11.6% termination of pregnancy. Severe non-chromosomal congenital heart defects – excluding ventricular septal defects, atrial septal defects, and pulmonary valve stenosis – occurred in 2.1 per 1000 births, of which 10.3% were perinatal deaths, 59.1% prenatally diagnosed, and 24.3% termination of pregnancy. Of the severe congenital heart defects, the rates of single ventricle (0.20‰), Ebstein anomaly (0.11‰), common arterial trunk (0.25‰), and atrioventricular septal defect (0.62‰) exceeded averages found in Europe, although coarctation of the aorta was infrequent. Conversely, rates of ventricular septal defects, atrial septal defects, and pulmonary valve stenosis were inferior to European standards. Slightly less than half of the congenital heart defects of chromosomal origin were associated with Down syndrome. *Conclusion:* In La Réunion, the total prevalence of congenital heart defects is far inferior to that found in Europe. The difference can be attributable to lower prevalences of mild congenital heart defects.

Keywords: Congenital heart disease; malformation; epidemiology; prevalence; neonate

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Congenital malformations occur in approximately 2–3% of overall births,[1,2] of which congenital heart defects represent the most frequent type. Prevalence rates of congenital heart defects are very variable, ranging from 4 to 17 per 1000 of total births;[3,4] however, baseline rates are usually considered between 6 and 8 per 1000 live births.[3–8] Congenital heart defects are frequently associated with a chromosomal anomaly, such as Down syndrome, or with genetic syndromes, such as 22q11 micro-deletion, or with non-genetic syndromes, such as those resulting from teratogens. Congenital heart defects may also be associated with extra-cardiac birth defects, but most are non-chromosomal, although there is no description of definite causes of such inherited disorders.

Congenital heart defects are involved in 6% of perinatal mortality[9] and 12–22% of infant deaths,[10,11] which represent approximately half of the burden of infant mortality due to congenital malformations.[6,9] They are also a leading cause of termination of pregnancy for foetal anomaly.[7] In this light, congenital heart defects represent a public health concern with a heavy economic burden owing to the cost of initial surgery but also, for the most severe, because of lifelong consequences. It is therefore important to better understand their epidemiology and clinical presentation in order to better prevent their complications.

Worldwide, prenatal diagnosis for congenital heart defects is variable and sensitive to the repetition of prenatal ultrasonographies.[12] Thus, 56% of congenital heart defects associated with other malformations beneficiated prenatal diagnosis in countries recommending three ultrasonographies, but only 46% when only one unique ultrasonography is mandatory.[13] Such discrepancy may also depend on the type of the heart defect. Indeed, half of severe congenital heart defects such as hypoplastic left heart or single ventricle, for which the size of the ventricle is reduced, are diagnosed *in utero*, but only 5% of mild isolated ventricular septal defects.[14] Overall, in Europe, 19–48% of all congenital heart defects beneficiate a prenatal diagnosis.[15]

The purpose of this retrospective registry-based study was to describe the patterns of congenital heart defects on La Réunion island in order to make precise their prevalences, clinical features, the use of prenatal diagnosis, and related termination of pregnancy with regard to EUROCAT European standards.

Methods

Study location and participants

La Réunion is a French overseas department, located on a volcanic island of 2511 square kilometres, belonging to the Mascarene archipelago in the south-western Indian Ocean. It is characterised by a resilient sugarcane agriculture, a poor industrial development, and a service economy.

The population of La Réunion was formed during the last five centuries, principally comprising immigrant natives from Europe, Madagascar, India, East Africa, and China. It is a multi-ethnic and multi-cultural melting pot of 817,000 inhabitants, with approximately 14,500 births per year. Genetic mixing is important; however, the persistence of endogamy and inbreeding in some communities or small geographic isolates has led to increased rates of autosomal recessive disorders.[16]

The La Réunion island registry of congenital malformations was implemented as early as 2002. It collects information on all congenital birth defects diagnosed in the island, including live births, foetal deaths, stillbirths, and termination of pregnancy irrespective of the term, for epidemiological surveillance and research purposes. It is entrusted to the Association "Naître Aujourd'hui", which is a full member of the EUROCAT (European Registration of Congenital Anomalies and Twins) consortium, along with four other French regional registries. EUROCAT gathers the data from 42 European congenital malformations registries based in 20 European countries and monitors more than 1.5 million births per year.[17]

Data collection and classification

The case notification comes from public and private hospitals. Ascertainment is made by paediatricians and registry staff following extensive standardised chart reviews. Sources include maternity units, paediatric departments, prenatal diagnosis, anatomopathology, medical genetics, and cardiology units, as well as departments of medical information of hospitals. Cases are registered if diagnosed before birth, at birth, or during the first year of life. All infants with a congenital heart defect are followed up, but ascertainment may be incomplete if the malformation has not been diagnosed prenatally or during the hospital stay.

Early foetal death is recorded from the lower limit of 16 weeks of gestation, and stillbirth defined from the 20th week. Termination of pregnancy was introduced in La Réunion since 1975 and recorded from 2002. Autopsies were performed for unexplained foetal death, stillbirth, and termination of pregnancy.

Exposures of interest included occupation of mother and father, assisted reproduction, illness before and during pregnancy, and drug and teratogen intakes throughout pregnancy.

Congenital heart defects were defined according to the ICD-10 (International Classification of Diseases) classification and considered to be either of chromosomal origin (micro-deletions excluded), or non-chromosomal origin (micro-deletions, syndromes

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of non-chromosomal origin or related to drug or teratogen intake, or unexplained), as done within the EUROCAT consortium.

Patent ductus arteriosus was excluded.

The severity of the congenital heart defects was classified into three categories according to EUROCAT definition,[8] as shown in Table 1: SI (very severe), SII (severe without additional SI congenital heart defects), and SIII (mild, non-severe without additional SI or SII congenital heart defects). Other congenital heart defects of unknown severity were categorised as SIV (unclassified) with the exception of patent ductus arteriosus, which was excluded.

Each case of congenital heart defect was counted once for each given prevalence rate, that is, prevalence was based on cases, not on anomalies. Prevalence rates, expressed for 1000 births, were calculated as follows:

Live birth prevalence rate = (number of live birth cases) / (total births live and still)

Total prevalence rate = (number of live birth cases + number of foetal death cases + number of termination of pregnancy) / (total births live and still)

as done within the EUROCAT consortium.[8]

Statistical analysis

Proportions were compared using Chi-square or Fisher exact tests, as appropriate. We used Chi-square for linear trend tests for comparing proportions according to the congenital heart defects severity. Prevalence rates in La Réunion were compared with those found in Europe after exclusion of the observations originated from the island, using EUROCAT prevalence tables (www.eurocat-network.eu). Owing to the fact that La Réunion island is mainly of African and Asiatic descendence, benchmarking with African and Asiatic standards was also provided for the overall prevalence on literary grounds. Odds Ratios and 95% confidence intervals were calculated taking European prevalence rates as references. A p-value less than 0.05 was considered statistically significant. The statistical analyses were performed using Stata Software (release 11; StataCorp. 2009, Texas, United States of America).

Ethical statement

For the use of the data, oral consent was obtained from each parent or a first-degree relative, as the investigation was carried out under the standard care procedure, in accordance with the French law on biomedical research (art. 88-II, law 2004-806, Journal Officiel, 08/11/2004).

Table 1. Classification of CHD according to EUROCAT and CIM10.

ICD10	Severity type/subtype of CHD
	SI (very severe)
Q20.4	Single ventricle
Q22.4	Tricuspid atresia and stenosis
Q22.5	Ebstein anomaly
Q22.6	Hypoplastic right heart
Q23.4	Hypoplastic left heart
	SII (severe)
Q20.0	Common arterial trunk
Q20.1	Double-outlet right ventricle
Q20.2	Double-outlet left ventricle
Q20.3	d-Transposition of the great arteries
Q20.5	Discordant atrioventricular connection
Q20.6	Ivemark atrial isomerism
Q21.2	Atrioventricular septal defect
Q21.3	Tetralogy of Fallot
Q21.4	Aortopulmonary window
Q22.0	Pulmonary valve atresia
Q23.0	Aortic valve atresia or stenosis
Q20.8	Other abnormal cardiac connections
Q24.2	Cor triatriatum
Q24.4	Subaortic valve stenosis
Q24.5	Malformation of coronary arteries
Q25.1	Coarctation of the aorta
Q25.2	Interruption of aortic arch
Q25.3	Supravalvular aortic stenosis
Q26.2	Total anomalous pulmonary venous return
Q26.3	Partial anomalous pulmonary venous return
	SIII (mild, non-severe)
Q21.0	Ventricular septal defect
Q21.1	Atrial septal defect
Q22.1	Pulmonary valve stenosis
	SIV (unknown severity, unclassified)
Q22.2	Pulmonary valve congenital regurgitation
Q22.3	Other pulmonary valve regurgitation
Q22.8	Other tricuspid valve congenital malformations
Q22.9	Tricuspid valve congenital malformations without precision
Q23.1	Aortic valve bicuspid/aortic valve congenital regurgitation
Q23.2	Mitral valve stenosis or atresia
Q23.3	Mitral valve dysplasia
Q24.8	Congenital cardiac malformations
Q25.4	Other aortic malformations
Q25.7	Other pulmonary artery malformations
Q25.8	Other great arteries malformations

CHD = congenital heart defects; EUROCAT = European Registration of Congenital Anomalies and Twins; ICD = International Classification of Diseases

Results

Prevalence of congenital heart defects

Between January 1, 2002 and December 31, 2007, congenital malformations represented 26.73‰ (95% confidence interval: 26.56–29.90‰) of all births in La

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Réunion, including 2353 cases out of 88,025 births, live and still, of which 512 were diagnosed as cases of congenital heart defects (total prevalence rate of congenital heart defects cases: 5.82‰: 5.78–5.85‰). Congenital heart defects were the most frequent anomaly, accounting for 21.8% of all congenital birth defects. Of the 512 cases of congenital heart defects, 424 were live births (live birth prevalence rate: 4.80‰, 95% confidence interval: 4.78–4.83‰), five early foetal deaths, 13 stillbirths, and 70 terminations of pregnancy.

Classification of congenital heart defects

Of the 512 cases of congenital heart defects, 64 (12.5%) cases were associated with a chromosomal anomaly and 448 (87.5%) non-chromosomal. Of the 448 cases of congenital heart defects of non-chromosomal origin, 37 were associated with some additional extra-cardiac non-chromosomal anomalies. Out of these, 11 were associated with a micro-deletion, five attributed to various teratogen intakes, that is, alcohol, valproate, two cases each, and isotretinoin, one case, five to amniotic sequence, four to VATER/VACTERL syndrome, two with caudal regression syndrome, two with untyped nanism, one with Potter sequence, and seven unexplained.

Table 2 classifies all the congenital heart defects in order of decreasing prevalence and shows contributions of prenatal diagnosis and termination of pregnancy, for each of the three groups of severity.

The most frequent congenital heart defects type, irrespective of their chromosomal or non-chromosomal origin, was non-severe SIII congenital heart defects with 261 cases (51.0%), of which the predominant subtype was ventricular septal defects. Taken together, SIII congenital heart defects were less frequent in La Réunion than in the rest of Europe (2.97‰ versus 8.81‰, Odds Ratio: 0.58, 95% confidence interval: 0.51–0.66). Very severe SI congenital heart defects accounted for 12% of all congenital heart defects, of which the most prevalent was hypoplastic left heart. Single ventricle and Ebstein anomaly were more likely observed on the island (Odds Ratio: 3.70 and 2.53, respectively) than in Europe. SII congenital heart defects represented 33% of all congenital heart defects, with atrioventricular septal defects being the most prevalent. Other common SII included d-transposition of the great arteries, tetralogy of Fallot, common arterial trunk, and coarctation of the aorta. Common arterial trunk was more likely (Odds Ratio: 2.91) and coarctation of the aorta less frequently (Odds Ratio: 0.58) observed than in Europe.

In all, 21 (4.1%) congenital heart defects were of unknown severity and not classified.

The distribution of 448 congenital heart defects of non-chromosomal origin, of which 11 were linked to a micro-deletion, is shown in Table 3.

Overall, the severity of congenital heart defects differed according to their association with chromosomal anomalies. Severe SII congenital heart defects were more frequent in congenital heart defect cases associated with a chromosomal anomaly (64.1% versus 28.6% in non-chromosomal congenital heart defects, Chi-square test = 34.7, 2 degrees of freedom, $p < 0.001$).

SIII congenital heart defects represented 55% of the congenital heart defects of non-chromosomal origin, the predominant subtypes being ventricular septal defects – 47.3% of all congenital heart defects and atrial septal defect, 17.6%. SI congenital heart defects accounted for 12%, the most prevalent being hypoplastic left heart (4.9%). SII represented 29% of all non-chromosomal congenital heart defects, with atrioventricular septal defect and transposition of the great arteries being the most frequent (6.5%). Other common SII congenital heart defects were tetralogy of Fallot and coarctation of the aorta (3.8%, respectively) and common arterial trunk (3.4%). Severe (SI/SII) congenital heart defects – 40% of non-chromosomal congenital heart defects versus 28% in Europe – had a total prevalence of 2.06‰ (95% confidence interval: 2.05–2.07‰). Among these, the congenital heart defects exceeding significantly European standards were single ventricle (Odds Ratio: 3.05), Ebstein anomaly (Odds Ratio: 2.69), common arterial trunk (Odds Ratio: 2.27), and atrioventricular septal defect (Odds Ratio: 2.14). Conversely, the prevalence of coarctation of the aorta tended to be lower (Odds Ratio: 0.65, $p = 0.09$).

Out of the 11 cases of 22q11 micro-deletion, eight were associated with a SII congenital heart defects, two with a SIII, and one with a SI. The most frequent congenital heart defect was common arterial trunk with four cases – 36% of the congenital heart defects associated with 22q11 micro-deletion, followed by tetralogy of Fallot (two cases).

Of the 64 congenital heart defects of chromosomal origin, 32 (50%) were the consequence of Down syndrome, of which none had SI, 24 (75%) had SII, and 8 (25%) an SIII congenital heart defects. The most frequent congenital heart defect linked to Down Syndrome was atrioventricular septal defect (65.6%). No coarctation of the aorta was associated with Turner syndrome.

Factors associated with congenital heart defects

Overall, the sex ratio of the foetuses harbouring a congenital heart defect was in favour of males (52% versus 48% in females). Moreover, the severity of the congenital heart defect was greater in males (male proportion: SI: 64%, SII: 57%, and SIII: 48%, Chi-square for trend analysis for proportions: 9.2, 2 degrees of freedom, $p = 0.01$). This pattern persisted in non-chromosomic congenital heart defects.

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Table 2. CHD of chromosomal and non-chromosomal origin, La Réunion island, 2002–2007.

ICD10	Severity type/subtype of CHD	Total	Prevalence per 1000 (95% CI)	LB	FD	PD	TOPFA	TOPFA/PD (%)	TOPFA prevalence per 1000 (95% CI)
	SI (very severe)[¶]	61	0.693 (0.690–0.696)	29	3	52	29	55.8	0.329 (0.326–0.333)
Q.234	Hypoplastic left heart	26	0.295 (0.292–0.296)	10	1	22	15	68.2	0.170 (0.168–0.173)
Q.204	Single ventricle	18	0.204 (0.202–0.207)***	7	1	18	10	55.6	0.114 (0.112–0.116)
Q.225	Ebstein anomaly	10	0.114 (0.112–0.116)***	8	1	6	1	16.7	0.011 (0.011–0.012)
Q.224	Tricuspid atresia or stenosis	6	0.068 (0.066–0.070)	3	0	5	3	60.0	0.034 (0.033–0.035)
Q.226	Hypoplastic right heart	3	0.034 (0.033–0.035)	2	0	3	1	33.3	0.011 (0.011–0.012)
	SII (severe)[†,¶]	169	1.920 (1.911–1.922)	129	9	84	31	36.9	0.625 (0.622–0.628)
Q.212	Atrioventricular septal defect	55	0.625 (0.622–0.628)***	32	5	39	18	46.2	0.204 (0.011–0.012)
Q.203	d-Transposition of the great arteries	33	0.375 (0.372–0.378)	22	2	25	9	36.0	0.102 (0.100–0.104)
Q.213	Tetralogy of Fallot	24	0.273 (0.270–0.276)	21	1	10	2	20.0	0.023 (0.022–0.024)
Q.200	Common arterial trunk	22	0.250 (0.247–0.253)***	8	0	16	14	87.5	0.159 (0.157–0.161)
Q.251	Coarctation of the aorta	17	0.193 (0.191–0.196)*	16	0	5	1	20.0	0.011 (0.011–0.012)
Q.262	Total anomalous pulmonary venous return	4	0.045 (0.044–0.047)	3	0	2	1	50.0	0.011 (0.011–0.012)
Q.220	Pulmonary valve atresia	3	0.034 (0.033–0.035)	2	0	3	1	33.3	0.011 (0.011–0.012)
Q.230	Aortic valve atresia or stenosis	3	0.034 (0.033–0.035)	2	1	1	0	0.0	0.000
	SIII (mild, non-severe)[‡,¶]	261	2.965 (2.949–2.981)	251	4	39	6	15.4	0.068 (0.066–0.070)
Q.210	Ventricular septal defect	227	2.579 (2.565–2.592)**	215	2	42	10	23.8	0.114 (0.112–0.116)
Q.211	Atrial septal defect	85	0.966 (0.964–0.967)***	76	3	18	6	33.3	0.068 (0.066–0.070)
Q.221	Pulmonary valve stenosis	17	0.193 (0.191–0.196)**	17	0	4	0	0.0	0.000
	SIV (unknown severity)[#,¶]	21	0.239 (0.236–0.241)	15	2	12	4	33.3	0.045 (0.044–0.047)
	Total	512	5.817 (5.782–5.851)**	424	18	187	70	37.4	0.795 (0.793–0.798)

CHD = congenital heart defects; CI = confidence interval; FD = foetal deaths (including 5 early foetal deaths and 13 stillbirths); ICD = International Classification of Diseases; PD = prenatal diagnosis; TOPFA = terminations of pregnancy for foetal anomaly; LB = livebirths

Data are given as numbers, percentages, and ‰ calculated over 88,025 total births live and still

[¶]Each type totalises the number of foetuses with a CHD, each subtypes totalises the exact number of CHD (as done on EUROCAT prevalence tables), so that the sum of subtypes cannot match the type number, the difference corresponding to foetuses combining multiple CHD

[†]Severe SII CHD are defined without additional SI CHD

[‡]Mild SIII CHD are defined without additional SI or SII CHD

[#]Data on diagnoses Q22.2, Q22.3, Q22.8, Q23.1, Q23.2, Q23.3, Q24.8, Q25.4, Q25.7, Q.25.8 are pooled

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, not significant if not stated. Comparison with EUROCAT prevalence tables (Réunion excluded) as references

Table 3. CCHD of non-chromosomal origin (chromosomal causes excluded), La Réunion island, 2002–2007.

ICD10	Severity type/subtype of CHD	Total	Prevalence per 1000 (95% CI)	LB	FD	PD	TOPFA	TOPFA/PD (%)	TOPFA prevalence per 1000 (95% CI)
	SI (very severe)[¶]	53	0.602 (0.599–0.605)	26	2	45	25	55.6	0.284 (0.281–0.287)
Q.234	Hypoplastic left heart	22	0.250 (0.247–0.253)	8	1	19	13	68.4	0.148 (0.145–0.150)
Q.204	Single ventricle	14	0.159 (0.157–0.161)***	6	0	14	8	57.1	0.091 (0.089–0.093)
Q.225	Ebstein anomaly	10	0.114 (0.112–0.116)***	8	1	6	1	16.7	0.011 (0.011–0.012)
Q.224	Tricuspid atresia or stenosis	6	0.068 (0.066–0.070)	3	0	5	3	60.0	0.034 (0.033–0.035)
Q.226	Hypoplastic right heart	3	0.034 (0.033–0.035)	2	0	3	1	33.3	0.011 (0.011–0.012)
	SII (severe)[†,¶]	128	1.454 (1.449–1.460)	103	6	62	19	30.6	0.216 (0.213–0.219)
Q.212	Atrioventricular septal defect	29	0.329 (0.326–0.333)***	18	2	23	9	39.1	0.102 (0.100–0.104)
Q.203	d-Transposition of the great arteries	29	0.329 (0.326–0.333)	20	2	22	7	31.8	0.080 (0.078–0.081)
Q.213	Tetralogy of Fallot	17	0.193 (0.191–0.196)	15	1	8	1	12.5	0.011 (0.011–0.012)
Q.251	Coarctation of the aorta	17	193 (0.191–0.196)	16	0	5	1	20.0	0.011 (0.011–0.012)
Q.200	Common arterial trunk	15	0.170 (0.168–0.173)**	3	0	12	12	100.0	0.136 (0.134–0.139)
Q.230	Aortic valve atresia or stenosis	3	0.034 (0.033–0.035)	2	1	1	1	100.0	0.011 (0.011–0.012)
Q.262	Total anomalous pulmonary venous return	2	0.023 (0.022–0.024)	1	0	1	1	100.0	0.011 (0.011–0.012)
Q.220	Pulmonary valve atresia	1	0.011 (0.011–0.012)	1	0	1	0	0.0	0.000
	SIII (mild, non-severe)[‡,¶]	247	2.806 (2.791–2.821)	239	4	31	4	12.9	0.045 (0.044–0.047)
Q.210	Ventricular septal defect	212	2.408 (2.396–2.421)*	202	2	33	8	24.2	0.091 (0.089–0.093)
Q.211	Atrial septal defect	79	0.897 (0.895–0.899)***	71	3	15	5	33.3	0.057 (0.055–0.058)
Q.221	Pulmonary valve stenosis	17	193 (0.191–0.196)*	17	0	4	0	0.0	0.000
	SIV (unknown severity)[#,¶]	20	0.227 (0.224–0.230)	14	2	11	4	36.4	0.045 (0.044–0.047)
	Total	448	5.089 (5.059–5.120)	382	14	149	52	34.9	0.591 (0.587–0.594)

CHD = congenital heart diseases; CI = confidence interval; FD = foetal deaths (including 4 early foetal deaths and 10 stillbirths); ICD = International Classification of Diseases; PD = prenatal diagnosis; TOPFA = terminations of pregnancy for foetal anomaly; LB = livebirths

Data are given as numbers, percentages, and ‰ calculated over 88,025 total births live and still

[¶]Each type totalises the number of foetuses with a CHD, each subtypes totalises the exact number of CHD (as done on EUROCAT prevalence tables), so that the sum of subtypes cannot match the type number, the difference corresponding to foetuses combining multiple CHD

[†]Severe SII CHD are defined without additional SI CHD

[‡]Mild SIII CHD are defined without additional SI or SII CHD

[#]Data on diagnoses Q22.2, Q22.3, Q22.8, Q23.1, Q23.2, Q23.3, Q24.8, Q25.4, Q25.7, Q.25.8 are pooled

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, not significant if not stated. Comparison with EUROCAT prevalence tables (Réunion excluded) as references

For non-chromosomal congenital heart defects, the mean age of mothers was 28.0 years (95% confidence interval: 27.4–28.7 years) and the mean age of progenitors was 32.2 years (95% confidence interval: 31.2–33.1 years).

Occupation of mothers or progenitors, assisted reproduction technologies, and drug and teratogen intakes during pregnancy could not be linked to congenital heart defects because of incomplete data.

Survival and impact on perinatal mortality of congenital heart defects

Of 382 live births with non-chromosomal congenital heart defects, 97% were alive after day 6, with survival being linked to the severity of the congenital heart defect: 81% in SI, 97% in SII, and 99% in SIII (Chi-square for trend: 20.6, 2 degrees of freedom, $p < 0.001$). Non-chromosomal congenital heart defects represented 1% of stillbirths and 3% of perinatal deaths.

Contribution of prenatal diagnosis and termination of pregnancies

The diagnosis of congenital heart defects was made for 37% *in utero* – 33.3% when chromosomal congenital heart defects were excluded. Approximately 70% of prenatal diagnosis was performed from 22 weeks of gestation. For non-chromosomic congenital heart defects, the rate of prenatal diagnosis increased with the severity of the congenital heart defects: 85% in SI, 48% in SII, and 13% in SIII (Chi-square for trend analysis of proportions: 126.5, 2 degrees of freedom, $p < 0.001$). When congenital heart defects were of chromosomal origin, these rates were of 88%, 54%, and 57%, respectively.

The rate of terminations of pregnancy – 13.7% for all congenital heart defects – was linked to the severity of the congenital heart defects: 48% of SI congenital heart defects underwent a termination of pregnancy, 18% of SII but only 2% of SIII, of whom six cases were multiple congenital heart defects (Chi-square for trend analysis for proportions: 88.9, 2 degrees of freedom, $p < 0.001$). These become 56%, 37%, and 15% if the congenital heart defects was diagnosed prenatally. For non-chromosomal congenital heart defects, the rate of termination of pregnancy was 12%. After prenatal diagnosis in non-chromosomic congenital heart defects, we observed the same trend: 56% in SI, 31% in SII, and 13% in SIII (Chi-square for trend: 15.4, 1 degrees of freedom, $p < 0.001$).

Discussion

Here we report the total prevalence of congenital heart defects during 2002–2007 of 5.8‰, with some annual variations ranging between 5.2‰ in 2004 and 6.8‰ in 2006. This burden is far lower than those usually found in Europe,[8] for which the average prevalence is 8.0‰ (95% confidence interval: 7.9–8.1‰).[8] It is also far inferior to that observed at a community-level sonography screening in China (18.7‰).[18] To the best of our knowledge, it would be closer to those found in India or Africa, where the lack of national registries and population-based surveys hampers such a comparison, while a residual proportion of home births and early neonatal/infant deaths still encourages studies on skewed populations such as school or at-risk children.[19–22] The difference may be due first to underascertainment and/or underreporting in the frame of asymptomatic non-chromosomal SIII/SIV congenital heart defects: newborns for whom the diagnosis of such mild congenital heart defects was not made prenatally or at first-day examination, or who did not require hospitalisation, could therefore have escaped surveillance, as suspected with lower ventricular septal defect, atrial septal defect, and pulmonary valve stenosis rates. Furthermore, we did not include patent ductus arteriosus, which may also feature a significant burden of congenital heart defects in certain studies.[4] Second, La Réunion is far less exposed to air pollutants (carbon monoxide, ozone, particulate matter inferior than 10 micrometres), some of the congenital heart defects risk factors recognised in recent years,[23,24] as a consequence of poor industrial development and regular air cleansing by sea salt and trade-winds (Observatoire Réunionnais de l'Air: http//www.atmo-reunion.net). Indeed, sulphur dioxide, the only pollutant sometimes measured in excess on the island, often at the peak of intense volcanic activity, have produced conflicting results regarding early exposure during pregnancy and the subsequent rise in congenital heart defects: it was thus associated with higher rates of ventricular septal defect in Texas,[25] but also with low prevalences of patent ductus arteriosus and congenital heart defects in the United Kingdom.[26] Third, tobacco smoking during pregnancy, another contributor of oxidative stress for the embryo, may be unusually low in La Réunion (11.5%) compared with western standards (up to 20%).[27] Prenatal exposure to environmental toxicants, such as major air pollutants or tobacco, is well known to alter the balance of factors turning on and off gene transcription, to cause a wide range of genetic dysfunctions that are expressed early in the embryo or even later into infancy;[28] their prevention by a "cleaner environment" could therefore lower the extent of congenital cardiac defects on a regional basis. Such a low prevalence of congenital heart defects in La Réunion is even more surprising that the reproductive population on the island combines several other

conditions that should promote congenital heart defects, such as for instance a high rate of mothers (and fathers) aged over 40 years (4%),[29,30] consanguinity,[16,31] increasing proportion of obesity (11.7%), and gestational diabetes (7.5%),[32–35] and, by extent, a rising underestimation of pre-gestational diabetes,[35] as previously shown in grand multipara.[36] The low burden of congenital heart defects among live births is not counterbalanced by higher rates in stillbirths and termination of pregnancies. Interestingly, the total prevalence of severe (SI/SII) non-chromosomal congenital heart defects in our population (2.06‰) superposes that encountered in Europe (2.03‰), whereas the proportion of (SI/SII) is greater (40% versus 28%), leading to consider non-chromosomal SIII (48.2% of all congenital heart defects) as the key to explain the low overall prevalence on the island. However, in our retrospective survey, we were unable to decipher the proportion of non-chromosomal SIII congenital heart defects diagnosed after the first week of life, and thus the contributions of underascertainment/underreporting and risk/protective factors to the toll of congenital heart defects in La Réunion deserves further investigation. Considering the specific non-chromosomal congenital heart defects exceeding European standards, we notice that the prevalence of single ventricle (0.16‰) in La Réunion is threefold higher than that observed on average in Europe (0.05‰),[8] and twice those of other French registries (0.08‰ in Paris, 0.09‰ when pooling Auvergne and Alsace data); however, La Réunion is overcome only by Malta (0.21‰) at the top of European registries. We could not ascertain whether this rate could be linked to consanguinity or to type-1 diabetes, as evidenced previously in the literature.[37,38] In the same way, Ebstein anomaly (0.11‰) far exceeds the average rate observed in Europe (0.04‰) and northern America (0.05–0.07‰),[39,40] and La Réunion ranks at the second position in Europe after Paris registry (0.13‰).[8] However, we found here neither obvious history of twins, congenital heart defects in the family, previous miscarriage, benzodiazepine use, varnishing nor racial predisposition, advanced maternal age or seasonal conception associated with this right-sided malformation.[39,40] Similarly, common arterial trunk is far more prevalent on the island (0.17‰) than European (0.07‰) and French averages (0.04‰ in Paris, 0.09‰ in Auvergne/Alsace).[8] We hypothesise it could be explained first by good autopsy coverage, two-thirds of common arterial trunk undergoing termination of pregnancy which leads to autopsy. Second, increasing proportions of obese and older women may also play a role in our setting, as evidenced in Texas.[41] It is also remarkable that 22% of non-chromosomal common arterial trunk harbour the 22q11 micro-deletion, consistent with literature.[42] On the other hand, common arterial trunk represents 36% of the congenital heart defects associated with 22q11 micro-deletion, which is a unusually high proportion.[43] Another hallmark of the island is the burden of atrioventricular septal defects of non-chromosomal origin (0.33‰ versus 0.15‰ in Europe), which, with d-transposition of the great arteries, was the most common severe non-chromosomal congenital heart defect. Indeed, the picture represents more than half of the total of atrioventricular septal defects, whose majority is usually linked to Down syndrome.[44] Such a high prevalence of atrioventricular septal defect is overcome in Europe only in two registries (Hainaut, Belgium and Odense, Denmark).[8] We could not make evidence of any association between atrioventricular septal defects and maternal diabetes, antitussive use, familial history of congenital heart defects, or paternal exposure to ionising radiation.[45] For each of these severe non-chromosomal congenital heart defects, recording foetuses between the 16th and 20th week of gestation had no significant influence on prevalence rates and no geographic cluster was identified. Severe congenital heart defects were more likely to be observed in male offspring, as a putative consequence of increased oxidative stress in males.[46]

Conversely, we also report a lower prevalence (0.19‰) than European average of coarctation of the aorta. Although not statistically significant for non-chromosomal coarctation of the aorta, because of lack of statistical power, it was as much unexpected that we found a significant age difference between the parents of non-chromosomal congenital heart defects; this age discrepancy – with older fathers than mothers – is linked to coarctation of the aorta in the literature.[47] This finding cannot be explained by underascertainment, with most of symptomatic coarctation being diagnosed before the first birthday.

Globally, the percentage of 12.5% of the congenital heart defect cases associated with a chromosomal anomaly in La Réunion superposes that of 12% observed in Europe, whereas the proportion linked to Down syndrome (50.0%) is smaller on the island compared with the 58% on the continent.[8] Accordingly, we found here chromosomal anomalies less prominent among atrioventricular septal defects cases (47% versus 57%) than in Europe. The burden of atrioventricular septal defects in Down syndrome – nearly two-thirds of Down syndrome-related congenital heart defects – is more important in La Réunion than the upper limit of 45% observed in Europe.[44] The lesser contribution of Down syndrome to the burden of the congenital heart defects of chromosomal origin can be explained in our setting by higher proportions of other chromosomal anomalies associated with congenital heart defects, data not shown,

undergoing earlier assessment including foetuses before 20 weeks.

The first-week postnatal mortality of live births with non-chromosomal congenital heart defects was 3% in La Réunion in 2002–2007, and less than 2.5% on average in Europe in 2000–2005. This difference can be attributable to avoided transfers to Paris, where the heart surgery department is located, for ethical or economic purposes. However, the part of non-chromosomal congenital heart defects in first-week deaths, approximately 2% on the island, data not shown, superposed the rate of 2.3% found in Europe.[8] Similarly, the respective proportions of stillbirths and perinatal deaths in La Réunion were substantially equivalent (1% and 3%) to European standards (1.2% and 3.6%).[8]

Overall, more than two-thirds of the congenital heart defects beneficiated a prenatal diagnosis. This rate ranged from 12.5% in mild non-chromosomal SIII congenital heart defects to 87.5% for very severe chromosomal SI congenital heart defects, whereas 57.1% of SIII chromosomal congenital heart defects and 84.9% of non-chromosomal SI congenital heart defects underwent a prenatal diagnosis. This trend matches that found in other French registries.[1,9]

The contribution of termination of pregnancy to the diagnosis of congenital heart defects in our setting (13.7%) was superior to that observed on average in Europe (9.1%), but below the range of other French registries (15.9–24.7%).[8] Although, women and families might be more reluctant to termination of pregnancy in La Réunion because of strong religious beliefs, the difference to the European standard can first be explained by a higher proportion of non-chromosomal (SI/SII) congenital heart defects on the island (40.8%) than in Europe (28.3%).[8] Thus, the rate of termination of pregnancy for non-chromosomal (SI/SII) congenital heart defects was 24.3%, superior to that found on average in Europe (14.0%).[8] The use of termination of pregnancy depends either on the severity of the congenital heart defects on its syndromic character or not, or both. In our survey, the rate of termination of pregnancy after prenatal diagnosis for SI congenital heart defects was almost equivalent, whether the congenital heart defects were non-chromosomal (55.6%) or associated with a chromosomal anomaly (50.0%). This difference was enlarged for SII and SIII congenital heart defects (20% and 7%, respectively) for which the decision of termination of pregnancy relied more on the other anomalies associated. Finally, the rate of termination of pregnancy observed in La Réunion may also come from the absence of heart surgery department on the island and from the difficulties to transfer children to such a centre located 5800 miles away. Our study lends support to open a paediatric cardiac centre in La Réunion that could benefit to the whole Indian Ocean area population, or to further the collaborations with South Africa, which could be more cost effective and also interesting for international collaborative purposes.

Limitations

Given the retrospective nature of the data collection, we cannot guarantee the completeness of the declarations. The framework of daily perinatal survey on the island,[30,31,35,36] the coverage of the registry, and the awareness of its staff may, however, limit the scope of underreporting.

Conclusion

Between 2002 and 2007, the burden of congenital heart defects represented 5.8‰ of total births and 4.8‰ live births in La Réunion island. Of 424 live births with congenital heart defects, 60% were non-severe malformations, requiring simple medical and ultrasound surveillance during infancy and childhood. Prevalence of single ventricle, Ebstein anomaly, common arterial trunk, and atrial ventricular septal defect far exceeded averages observed in Europe, without evidence of any clusters, either familial or environmental, leading to an increase in the proportion of severe congenital heart defects. Coarctation of the aorta was infrequent. Although predominant, ventricular septal defects, atrial septal defects, and pulmonary valve stenosis were less prevalent than expected, leading to discuss under-ascertainment and underreporting, as well as a protective environment. Finally, on this island located to a 12-hour flight from a cardiac surgery centre, the use of prenatal diagnosis and termination of pregnancy complied satisfactorily to European standards.

This work provides valuable insights into the patterns of congenital heart defects in a tropical setting free of major air pollutant.

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