Cardiology in the Young

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The epidemiology of CHD in Malta

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Abstract

Background: CHD refers to structural cardiac abnormalities which comprise the commonest group of congenital malformations. Malta is a small island in the central Mediterranean with excellent diagnostic and therapeutic facilities. It is unique in the European population as termination of pregnancy is illegal. This study was carried out to ascertain patterns in CHD prevalence in comparison with EUROCAT data (European Surveillance of Congenital Anomalies). *Methods:* Anonymised data were obtained from the EUROCAT website for 1993–2020. *Results:* There were a total of 22,833,032 births from all EUROCAT Registries, of which 121,697 were from Malta. The prevalence rate for Malta CHD was 32.38/10,000 births (at the higher end of the range). Malta had a significant excess of commoner, comparatively non-severe CHDs. For most of the severe lesions analysed rates reported were higher than EUROCAT average, however, apart from Ebstein's anomaly, they all fell within the ranges reported from the different registries. *Discussion:* Wide variations in reported CHD prevalence are known, and the Malta rates may be higher for milder defects due to quicker pickup prior to spontaneous resolution. There may also be a higher pickup of milder forms of more severe conditions. For the more severe conditions, lack of termination may be the explanation. These factors may result in the higher neonatal mortality observed in Malta.

Epidemiological studies that deal with congenital malformations are vital as they allow not only for quantification but also for service planning. Moreover, the detection of clusters/outlier values may help to provide clues regarding aetiology/prevention. Specific conditions are mandatory for an epidemiological study dealing with congenital malformations to have validity and therefore utility. The catchment areas must be clearly defined with clearly identified referral routes for patients with suspected conditions, the methodology must be objective and reproducible, and there must be accurate record-keeping with precise registration.

The term "congenital heart disease" refers to structural abnormalities of the heart or great vessels that are actually or potentially of functional significance.[1]This is an umbrella term that encompasses a wide variety of lesions such that this is are commonest group of congenital malformations and has an overall birth prevalence of almost 10/10,000 live births.[1]

Malta is a small island in the central Mediterranean with a population of approximately half a million. Diagnostic and therapeutic interventions are introduced swiftly in CHD,[2] and a declining age in diagnosis and surgery has been shown to decrease mortality.[3,4]

While antenatal screening for congenital anomalies is universal in Malta via an anomaly scan at week 19–24 of pregnancy,[5] termination of pregnancy remains illegal and those seeking termination must go abroad.[5,6] Postnatally, paediatric echocardiography for diagnostic purposes is readily available with no waiting times at the only regional (state) hospital in Malta where almost all deliveries are carried out. Services are free at point of care (state funded from taxation similar to the United Kingdom National Health Service model).

An earlier study in this country conducted for the birth years 1990–1994 had shown that there was an excess of lesions causing right ventricular outflow tract obstruction,[7] especially tetralogy of Fallot.[8] Furthermore, despite the relatively small population size, there were no other excesses of conditions associated with CHD.[9]

This study was carried out in order to ascertain whether there are any unusual patterns in CHD prevalence in this somewhat unique population by comparing a longer term of Malta data with equivalent European data using data available from the EUROCAT database (European Surveillance of Congenital Anomalies). This was deemed an appropriate comparison as the definitions of EUROCAT are standardised as far as possible across all participating registries.[10]

The Malta Congenital Anomalies Registry is a full participating member of EUROCAT. The Malta Registry has full access to all public hospital paediatric echocardiogram reports thus having a good coverage and ascertainment of CHDs diagnosed in Malta.

Materials and methods

Anonymised data were obtained from the EUROCAT interactive database. EUROCAT is a high-quality network of population-based congenital anomaly registries across Europe for the

monitoring, surveillance, and research of congenital anomalies. This network was founded in 1979 and now comprises 43 member registries from 23 countries covering more than 25% of European births.[11] Since EUROCAT prevalence data are anonymised and publicly available, ethics approval was not sought and data protection was not applicable.

Data were available as live births, fetal deaths from 20 weeks gestation and terminations of pregnancy for fetal anomaly following prenatal diagnosis (TOPFA). Data were available by individual cardiac defect lesions for the countries and registries shown in Table 1, and for the conditions shown in Table 2 and data were divided into Maltese and non-Maltese births. The "severe" subgroup is as defined by EUROCAT and includes single ventricle, hypoplastic right heart, hypoplastic left heart, tricuspid valve atresia, Ebstein anomaly, common arterial truncus, double outlet right ventricle, double outlet left ventricle, complete and corrected transposition of the great arteries, atrioventricular septal defect, tetra- and pentalogy of Fallot, pulmonary valve atresia, tricuspid valve stenosis, aortic valve atresia/stenosis, mitral valve atresia/stenosis, coarctation of aorta, aortic atresia/interrupted aortic arch, total and partial anomalous pulmonary venous return, Ivemark atrial isomerism, aortopulmonary window, cor triatriatum, subaortic valve stenosis, supravalvular aortic stenosis, and malformations of the coronary arteries.[12] Some of these conditions may present later in life, especially in milder forms (e.g. partial anomalous pulmonary venous drainage), albeit still needing intervention.

Confidence intervals for rates were calculated using the equations of Fleiss.[13] Chi tests were performed using a bespoke Excel sheet.[14] A p value ≤ 0.05 was taken to represent a statistically significant result.

Results

This study analysed data available between 1993 and 2020. There were a total of 22,833,032 births in this study, 121,697 of which were from Malta. Rates (per 10,000 births) and p values for birth prevalence lesions for Malta versus for the rest of EUROCAT are shown in Table 1.

Using EUROCAT data, the overall prevalence of severe CHD for all EUROCAT registries 1993-2020 is reported as 19.62/ 10,000 births (with a wide variation of reported rates ranging from 33.30/ 10,000 in Wales to 7.95/10,000 in Southern Portugal). The prevalence rate for Malta being reported as 32.38/10,000 births (taken from EUROCAT website as at 26/04/2023).

When comparing Malta rates with all EU Registries average rates, Malta reports a significant excess of commoner, often comparatively non-severe CHDs including atrial septal defect, ventricular septal defect, pulmonary stenosis, patent ductus arteriosus, and aortic stenosis. For the more severe and rarer congenital heart conditions atrioventricular septal defect, Tetraology and Pentalogy of Fallot, Ebstein's anomaly, total anomalous pulmonary venous drainage, aortic atresia/interruption, and coarctation of aorta were found to be significantly higher.

While the Malta rates compare higher than the overall EU average rate, most fall within the range reported from the different registries (Table1). The anomalies that fall outside the range of reported rates are atrial septal defects, pulmonary valve stenosis, and Ebstein's anomaly. These are conditions known to be significantly affected by differences in practices and case ascertainment methods.

Table 1. Country/registry, years, and births supplied.

Country / registry	Years of births supplied	Total births
Styria – Austria	1993–2020	296364
Antwerp – Belgium	1993–2020	486853
Hainaut – Belgium	1993–2020	339394
Pleven – Bulgaria	1993–2020	29,220
Zagreb – Croatia	1993–2020	171013
Funen – Denmark	1993–2020	145592
Paris – France	1993–2020	817110
Auvergne – France	2002, 2005–2020	225539
Isle de la Reunion – France	2002–2020	272240
French West Indies – France	2009–2020	110404
Brittany – France	2011–2020	339745
Saxony-Anhalt – Germany	1993–2020	427223
Cork and Kerry – Ireland	1996–2020	221342
SE Ireland – Ireland	1997–2017	142607
Milan Area - Italy	2012–2020	255323
Trento – Italy	2014–2020	27,509
Emilia Romagna – Italy	1993–2020	919766
Tuscany – Italy	1993–2020	757707
Malta – Malta	1993–2020	121697
n Netherlands – NL	1993–2020	502123
Norway - Norway	1999–2020	1191012
Wielkopolska – Poland	1999–2019	782301
Poland – Poland	1999–2018	6144011
S Portugal – Portugal	1993–2019	460300
Basque Country – Spain	1993–2016	446542
Valencian Region – Spain	2007–2020	642384
Navarre – Spain	2013–2020	45,825
Vaud - Switzerland	1993–2020	219815
Ukraine – Ukraine	2005–2019	432177
Wales – United Kingdom	1998–2018	699610
Thames Valley – United Kingdom	1993–2020	538742
Wessex – United Kingdom	1994–2020	759649
East Midlands & South Yorkshire – United Kingdom	1998–2012, 2016–2020	1344125
Northern England – United Kingdom	2000–2020	661358
South West England – United Kingdom	2005–2020	776787
West Midlands – United Kingdom	2016–2020	338875
Yorkshire and Humber – United Kingdom	2016–2020	208135

Discussion

It is known that there are wide variations in reported prevalence of CHD between registries which are explained by variations in the inclusion of the more minor anomalies, e.g. atrial septal defect,

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Table 2. N and birth prevalence (per 10,000 births) for CHD lesions obtained from EUROCAT, for Malta and for the rest of EUROCAT (Data taken from EUROCAT as at 26/04/2023).

	Rest of EUROCAT							EUROCAT total prevalence range / 10,000 births		Malta only								
	LB N	FD N	TOPFA N	Total N	Rate	LCI	UCI	Lowest	Highest	LB N	FD N	TOPFA N	Total N	Rate	LCI	UCI	chi	p
CHDs	148654	2320	12,739	163713	72.08	71.74	72.43	32.00 (Southern Portugal)	129.06 (Vaud, Switzerland)	1799	30	0	1829	150.29	143.57	157.32	1028.6	<0.0001
Severe CHDs*	35,813	1093	7358	44,264	19.49	19.31	19.67	7.95 (Southern Portugal)	33.3 (Wales, United Kingdom)	383	11	0	394	32.38	29.3	35.77	103	<0.0001
Ventricular septal defect	71,937	745	3533	76,215	33.56	33.32	33.8	16.22 (Wessex, UK)	62.28 (Brittany, France)	663	10	0	673	55.3	51.25	59.67	170.5	<0.0001
Atrial septal defect	38,762	235	803	39,800	17.52	17.35	17.7	5.87(Southern Portugal)	61.14 (Styria, Austria)	803	11	0	814	66.89	62.42	71.67	1661.2	<0.0001
Pulmonary valve stenosis	7829	35	203	8067	3.55	3.48	3.63	1.52 (Southern Portugal)	13.31 (Navarre, Spain)	220	0	0	220	18.08	15.8	20.67	704	<0.0001
Coarctation of aorta	7085	128	416	7629	3.36	3.28	3.44	1.17 (Zagreb, Croatia)	5.88 (N. England, UK)	59	0	0	59	4.85	3.72	6.3	8	0.005
Atrioventricular septal defect	6921	306	2010	9237	4.07	3.98	4.15	1.74 (Southern Portugal)	9.51 (French West Indies, France)	76	4	0	80	6.57	5.25	8.23	18.6	<0.0001
Complete TGA (D-TGA)	6296	88	648	7032	3.1	3.02	3.17	1.52 (Southern Portugal)	4.80 (Navarre, Spain)	47	3	0	50	4.11	3.08	5.46	4	0.045
Tetralogy/pentatology Fallot	6080	148	793	7021	3.09	3.02	3.16	1.37 (Pleven, Bulgaria)	5.81 (Yorkshire and Humber, UK)	64	0	0	64	5.26	4.08	6.76	18.3	<0.0001
PDA (only CHD in term infants)	6047	0	0	6047	2.66	2.6	2.73	0.50 (Hainaut, Belgium)	10.50 (Norway)	55	0	0	55	4.52	3.44	5.93	15.6	<0.0001
Hypoplastic left heart	3202	156	2056	5414	2.38	2.32	2.45	1.07 (Valencia Region, Spain)	4.36 (Navarre, Spain)	30	3	0	33	2.71	1.9	3.86	0.5	ns
Aortic valve atresia/ stenosis	2653	36	229	2918	1.28	1.24	1.33	0.34 (Pleven, Bulgaria)	2.76 (Wales, UK)	28	0	0	28	2.3	1.56	3.37	9.7	0.002
Double outlet right ventricle	1915	89	579	2583	1.14	1.09	1.18	0.29 (Zagreb, Croatia)	2.98 (Yorkshire and Humber, UK)	8	0	0	8	0.66	0.31	1.35	3.8	ns
Pulmonary valve atresia	1703	42	427	2172	0.96	0.92	1	0.39 (Poland)	2.36 (Northern England, UK)	16	0	0	16	1.31	0.78	2.19	3.8	ns
Triscuspid atresia/ stenosis	1102	39	354	1495	0.66	0.63	0.69	0.25 (Poland)	1.37 (Northern Netherlands)	9	1	0	10	0.82	0.42	1.57	0.5	ns
Total anom. pulm. venous return	1097	5	67	1169	0.51	0.49	0.55	0.06 (Zagreb, Croatia)	1.37 (Pleven, Bugaria)	14	0	0	14	1.15	0.65	1.98	9.4	0.002
Common arterial truncus	1071	60	422	1553	0.68	0.65	0.72	0.28 (Southern Portugal)	3.42 (Pleven, Bugaria)	7	1	0	8	0.66	0.31	1.35	0	ns
Single ventricle	908	46	480	1434	0.63	0.6	0.67	0.18 (Cork and Kelly, Ireland)	1.84 (Isle de la Reunion - France)	13	0	0	13	1.07	0.59	1.88	3.6	ns
Ebstein's anomaly	778	62	117	957	0.42	0.4	0.45	0.11 (Southern Portugal)	0.88 (Isle de la Reunion - France)	22	1	0	23	1.89	1.23	2.89	60.8	<0.0001

(*Continued*)

Table 2. (*Continued*)

	Rest of EUROCAT						EUROCAT total prevalence range / 10,000 births	Malta only						
Mitral valve atresia/ stenosis	769	25	241	1035	0.46	0.43	0.48	0.12 (Zagreb, Croatia)	1.51 (Auvergne, France)	5	0	0	5	0.41	0.15	1.02	0.1	ns
Aortic atresia / interruption	642	19	169	830	0.37	0.34	0.39	0.06 (Wielkopolska - Poland)	1.33 (Auvergne, France)	11	0	0	11	0.9	0.48	1.67	9.5	0.002
Hypoplastic right heart	543	44	346	933	0.41	0.39	0.44	0.14 (Poland)	1.72 (French West Indies, France)	3	1	0	4	0.33	0.11	0.9	0.2	ns
Corrected TGA (L-TGA)	462	12	80	554	0.24	0.22	0.27	0.05 (Poland)	0.80 (West Midlands, UK)	3	0	0	3	0.25	0.06	0.79	0	ns
Double outlet left ventricle	73	1	44	118	0.05	0.04	0.06	0.0 (several Registries*)	0.27 (French West Indies, France)	2	0	0	2	0.16	0.03	0.66	2.9	ns

FD = fetal deaths/still births from 20 weeks gestation; LB = live births; TOPFA = termination of pregnancy for fetal anomaly following prenatal diagnosis; TGA = transposition of the great arteries.
*As defined by EUROCAT.[12]

small ventricular septal defects, pulmonary stenosis, as well as differences in the access to and waiting time for echocardiography.[12,15,16]

Efficient and intense screening increases the ability to pick up some of the smaller defects which may resolve spontaneously soon after such as small atrial septal defects and ventricular septal defects and minor pulmonary stenosis, resulting in increased reported rates of such self-resolving defects.

In Malta access to echocardiography is free for all residents and waiting time is negligible. Furthermore, all public hospital echocardiography reports are available to the Malta Congenital Anomalies Registry enabling a detailed and comprehensive national coverage of all CHD diagnosed on the Islands.[5]

The higher reported rates of relatively minor conditions such as atrial septal defect, entricular septal defect, and patent ductus arteriosus may be due to quick referral and diagnosis before spontaneous closure. Rapid referral and diagnosis also apply to minor pulmonary valve flow acceleration which resolves over time.[3] For the more severe conditions, there may be higher pickup of milder forms such as coarctation of the aorta and Ebstein's anomaly which would tend to inflate Malta's numbers.[3]

Malta is unique when compared to other EUROCAT Registers in that TOPFA is illegal.[5] Thus, the apparently higher rate of other, more severe CHD may be partially explained by the fact that in EUROCAT registries where TOPFA is practiced, terminations for antenatally diagnosed syndromes may not have had their CHD diagnosed and these defects would not be registered. It is conceivable that syndromes, including trisomies which are inherently associated with atrioventricular septal defects and 22q11 microdeletions which are associated with truncus and aortic arch anomalies, would not be registered as terminated due to their cardiac lesion but due to the syndrome, and the CHD will not be present in the available EUROCAT congenital heart defects listings. This potential source of bias has been noted in previous studies.[17,18]

Another potential explanation for the higher reported rates may be the centralisation of services in the only two public hospitals, with deliveries followed by echocardiograms when necessary, typically prior to hospital discharge, as well as the access of the Malta Registry to these results.[3]

While significantly higher rates were found when comparing Malta rates with EUROCAT average rates, when considering the wide variation of rates between Registries Malta registered highest rates only for the minor conditions of atrial septal defect, pulmonary valve stenosis, and Ebstein's anomaly (Table 1). Indeed, overall, for severe CHD as defined by EUCOCAT, the prevalence rate for Malta was 32.38/10,000 births, within the extant EUROCAT data range (7.95 in S. Portugal to 33.3/10,000 births in Wales) (taken from EUROCAT website as at 26/04/2023). Maltese rates would naturally fall were TOPFA legal especially since the antenatal diagnosis of congenital malformations is on par with that of other centres.[5]

An interrogation of the Maltese Paediatric Cardiology database showed that almost all children with univentricular hearts went down the univentricular palliation route to total cavopulmonary connection, except for hypoplastic left heart (no family opted to go down the Norwood route and the patients succumbed after a few days on ductal closure with palliative care) or with very complex isomerism sequences.[19] Those that had surgery all had their interventions in tertiary centres in the United Kingdom, with declining perioperative mortality rates and overall excellent results.[4] However, this type of surgery carries a high risk for

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long-term morbidity, mortality, poor clinical outcomes, and eventually poor quality of life when patients reach the stage of "failing Fontan",[20] inevitably incurring significant costs to both Malta's healthcare system as well as that of the reference surgical centres, with potential need for heart/heart-liver transplantation.[21]

Conclusion

It is relatively easy to study rates of conditions in countries with efficient and centralised services and effective record-keeping; however, caution is still required in the interpretation of these rates. In spite of best efforts at harmonisation, wide variation in reported rates of CHD persists between registries especially for the less severe defects, the diagnosis of which is significantly influenced by differences in clinical practices and case ascertainment. Furthermore, non-termination results in higher congenital malformation rates at birth and indeed, a previous study for 1994–2013 had shown that these accounted for 36.7% of the neonatal deaths and the proportionate neonatal mortality attributed to congenital anomalies was the highest reported from Europe.[6]

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