

Prenatal diagnosis of severe structural congenital malformations in Europe

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KEYWORDS: congenital malformation; prenatal diagnosis; termination of pregnancy

ABSTRACT

Objectives To assess at a population-based level the frequency with which severe structural congenital malformations are detected prenatally in Europe and the gestational age at detection, and to describe regional variation in these indicators.

Methods In the period 1995–1999, data were obtained from 17 European population-based registries of congenital malformations (EUROCAT). Included were all live births, fetal deaths and terminations of pregnancy diagnosed with one or more of the following malformations: anencephalus, encephalocele, spina bifida, hydrocephalus, transposition of great arteries, hypoplastic left heart, limb reduction defect, bilateral renal agenesis, diaphragmatic hernia, omphalocele and gastroschisis.

Results The 17 registries reported 4366 cases diagnosed with the 11 severe structural malformations and of these 2300 were live births (53%), 181 were fetal deaths (4%) and 1863 were terminations of pregnancy (43%); in 22 cases pregnancy outcome was unknown. The overall prenatal detection rate was 64% (range, 25–88% across regions). The proportion of terminations of pregnancy varied between regions from 15% to 59% of all cases. Gestational age at discovery for prenatally diagnosed cases was less than 24 weeks for 68% (range, 36–88%) of cases. There was a significant relationship between high prenatal detection rate and early diagnosis ($P < 0.0001$). For individual malformations, the prenatal detection rate was highest for anencephalus (469/498, 94%) and lowest for transposition of the great arteries (89/324, 27%).

Termination of pregnancy was performed in more than half of the prenatally diagnosed cases, except for those with transposition of the great arteries, diaphragmatic hernia and gastroschisis, in which 30–40% of the pregnancies with a prenatal diagnosis were terminated.

Conclusion European countries currently vary widely in the provision and uptake of prenatal screening and its quality, as well as the 'culture' in terms of decision to continue the pregnancy. This inevitably contributes to variation between countries in perinatal and infant mortality and in childhood prevalence and cost to health services of congenital anomalies. Copyright © 2004 ISUOG. Published by John Wiley & Sons, Ltd.

INTRODUCTION

Major congenital malformations are reported in at least 2% of all fetuses and infants¹ and have a major impact on perinatal and infant mortality and morbidity in infancy and childhood. During the last decades an increasing number of congenital malformations have been diagnosed prenatally by ultrasound investigations^{2–4}. Most previous published studies have focused on selected hospitals where the procedures undertaken have been clearly described according to research protocols. This paper, in contrast, considers the outcome of prenatal screening at the population level.

One of the purposes of prenatal diagnosis is to increase the possibility of optimal management of the pregnancy in terms of antenatal care, referral for birth to the required

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specialist level and planning of the postnatal treatment of the baby. Intrauterine treatment of the fetus for certain malformations has been attempted but until now with disappointing results⁵. In most European countries parents may opt for termination if one or more severe malformations are diagnosed in the fetus.

The aim of this study was to assess at a population-based level the frequency with which severe structural congenital malformations are detected prenatally in Europe and the gestational age at detection, and to describe regional variation in these indicators.

METHODS

Data were routinely collected from 17 European registries (Figure 1) of congenital malformations (EUROCAT: European Surveillance of Congenital Anomalies) for births covering the years 1995–1999. The EUROCAT registries are population-based and the geographically defined populations and the methods of case ascertainment of EUROCAT are described elsewhere¹. For further details on population coverage see the registry description for each EUROCAT member registry⁶. The registries are all based on multiple sources of information, including hospital records, birth and death certificates and post-mortem examinations, and include information about live births, fetal deaths with gestational age ≥ 20 weeks and induced abortions after prenatal diagnosis of malformations. All structural malformations, syndromes and chromosomal anomalies are included in the database except minor malformations according to a list of exclusion criteria.

Malformations are coded according to ICD/BPA 9 or ICD10. The information regarding each case includes type of birth, time of diagnosis (pre or postnatal) and,

for prenatal diagnosis, gestational age at discovery, gestational age at birth/abortion and final diagnosis. The EUROCAT database only includes information on time of diagnosis of the first malformation diagnosed, so for cases with more than one malformation it is not known which was the first diagnosed.

The selection of the 11 malformations included in this study were based on three criteria: the malformation should be one of the defined EUROCAT subgroups based on ICD/BPA9 and ICD10 codes, it should be potentially detectable by prenatal ultrasound investigation and it should be a sufficiently severe malformation that termination of pregnancy would be considered as an option. Based on these criteria the following 11 structural malformations were selected: anencephalus, encephalocele, spina bifida, hydrocephalus, transposition of great arteries, hypoplastic left heart, limb reduction defect, bilateral renal agenesis, diaphragmatic hernia, omphalocele and gastroschisis. Down syndrome has been analyzed separately⁷. We included all registries in which diagnosis was prenatally or postnatally known in more than 80% of the cases with the 11 malformations; 17 registries fulfilled these criteria. Of these, 14 registries reported cases with congenital malformations delivered in the period 1995–1999, two registries (Bulgaria and Campania, Italy) reported cases for the period 1996–1999 and Wales reported cases with congenital malformation for the years 1998–1999. The total number of births covered in the 17 registries was 1 198 519. This study population overlaps with the EUROSCAN study population² for nine registries in the period 1996–1998 (registries contributing for a total of 9–30 months).

Descriptive data are presented as percentages. Comparisons were performed using chi-square statistics and the Mann–Whitney test.

RESULTS

The 17 registries reported 4366 cases diagnosed with the 11 severe malformations during the study period. There were 2300 livebirths (53%), 181 fetal deaths (4%) and 1863 terminations of pregnancy (43%); in 22 cases the pregnancy outcome was unknown. Among the 4366 cases 4180 had one of the selected 11 malformations, 171 cases had two and 15 cases had three. Time of diagnosis was known for 4278/4366 cases (98%) and 2806/4366 (64%) were diagnosed prenatally. Among the 2806 prenatally diagnosed cases 849 were live births (30%), 91 were fetal deaths (3%) and 1863 were terminations of pregnancy (66%); there were three cases with type of birth recorded as unknown.

Regional data

The distribution of cases among registries, number of cases diagnosed prenatally and number of terminations of pregnancy are presented in Table 1. The proportion of prenatally diagnosed cases varied from 25% of the cases in Croatia to 88% of the cases in Paris. The proportion

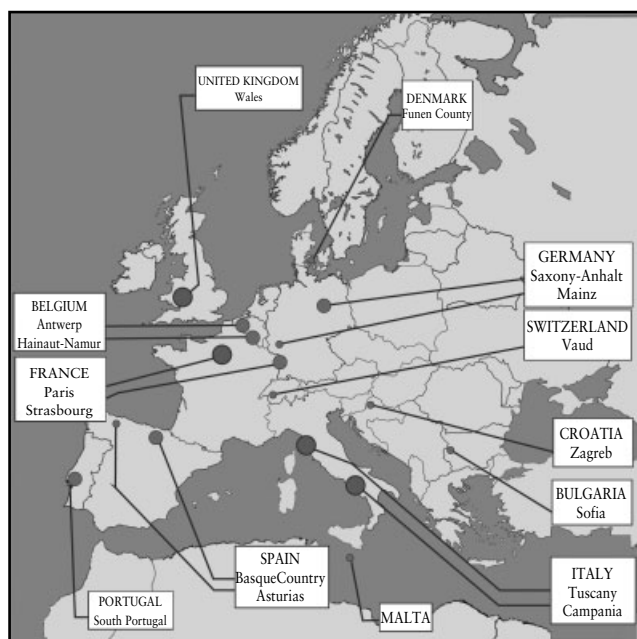


Figure 1 Map of Europe showing the location of the 17 registries of congenital malformations involved in the study.

Table 1 Data on number of cases, prevalence, prenatal diagnosis and terminations of pregnancy from 17 European regions reporting 11 severe malformations, 1995–1999*

Region†	Country	Total births	Cases (n)	Total prevalence per 1000 births	Time of diagnosis known (n (%))	Prenatal diagnosis (n (%))	Terminations of pregnancy (n (%))‡	Ratio terminations/ prenatal diagnosis	Terminations per 1000 births
Antwerp	BE	75 875	229	3.02	188 (82)	99 (43)	65 (28)	0.66	0.86
Hainaut	BE	60 804	191	3.14	191 (100)	127 (66)	80 (42)	0.63	1.32
Sofia	BG	38 257	169	4.42	162 (96)	47 (28)	27 (16)	0.57	0.71
Croatia	HR	31 255	53	1.70	51 (96)	13 (25)	9 (17)	0.69	0.29
Funen County	DK	28 953	102	3.52	102 (100)	38 (37)	15 (15)	0.39	0.52
Paris	F	188 388	1009	5.36	992 (98)	887 (88)	592 (59)	0.67	3.14
Strasbourg	F	67 158	302	4.50	301 (100)	213 (71)	157 (52)	0.74	2.34
Mainz	D	17 870	163	9.12	163 (100)	109 (67)	25 (15)	0.23	1.40
Saxony-Anhalt	D	48 295	216	4.47	203 (94)	109 (50)	87 (40)	0.80	1.80
Campania	I	196 081	522	2.66	522 (100)	263 (50)	217 (42)	0.83	1.11
Tuscany	I	125 188	249	1.99	248 (100)	145 (58)	104 (42)	0.72	0.83
Malta	MT	23 325	92	3.94	92 (100)	36 (39)	—	—	—
South Portugal	P	80 050	172	2.15	168 (98)	74 (43)	33 (19)	0.45	0.41
Asturias	E	32 370	127	3.92	127 (100)	83 (65)	62 (49)	0.75	1.92
Basque Country	E	80 882	279	3.45	278 (100)	187 (67)	140 (50)	0.75	1.73
Vaud	CH	37 892	134	3.54	134 (100)	92 (69)	66 (49)	0.72	1.74
Wales	UK	65 876	357	5.42	356 (100)	284 (80)	184 (52)	0.65	2.79
Total		1 198 519	4366	3.64	4278 (98)	2806 (64)	1863 (43)	0.66	1.55

All percentages are of total number of cases. *Bulgaria and Campania reported cases in 1996–1999 and Wales reported cases in 1998–1999. †For further details on population coverage see <http://www.eurocat.ulster.ac.uk/memberreg>. ‡Termination of pregnancy not legal in Malta. Gestational age limit for termination of lethal anomalies is 24 weeks in Belgium, Italy, Switzerland; 22 weeks in Spain; no upper limit in remaining countries; not known in Bulgaria²². For non-lethal serious anomalies, a different gestational age limit of 24 weeks is set in Croatia, Denmark and Portugal.

of terminations of pregnancy varied from 15% of all cases in Funen County and Mainz to 59% of all cases in Paris. There was also considerable regional variation in the number of terminations per 1000 births of these 11 malformations, ranging from 0.29 per 1000 births in Croatia to 3.14 per 1000 births in Paris. Termination of pregnancy is not allowed in Malta.

Among three regions (Funen County, Mainz and South Portugal) termination of pregnancy was performed in 23–45% of the cases diagnosed prenatally (73/221, 33%). In the other 13 regions (excluding Malta) it was done in 57–83% of the cases diagnosed prenatally (1790/2585, 69%).

In 13 of the 17 regions more than half of the prenatally diagnosed cases were diagnosed before 24 weeks of gestation (Table 2). Three registries (Antwerp, Tuscany and South Portugal) had a rather high proportion of cases with unknown gestational age at discovery. Less than 50% of the prenatally diagnosed cases were diagnosed before 24 weeks in Bulgaria, Croatia, Mainz and Malta. The best detection rate before 24 weeks was seen in Wales (88% of prenatally diagnosed cases). There was a significant relationship between high prenatal detection rate and early diagnosis, as the six regions with a less than 50% prenatal detection rate (Antwerp, Bulgaria, Croatia, Funen County, Malta and South Portugal) diagnosed 150 of 307 (49%) prenatally diagnosed cases before 24 weeks compared with the 11 regions with a higher prenatal detection rate, where 1764 of 2499 prenatally diagnosed cases (71%) were diagnosed before

24 weeks ($P < 0.0001$). Eleven percent of terminations of pregnancy were performed at 24 weeks or later and 141 of these 212 late terminations were from the two French registries.

Malformation data

Table 3 shows the proportions of cases prenatally diagnosed and also those ending in termination of pregnancy, for the 11 malformations. The vast majority of cases, except for omphalocele, were not associated with chromosomal abnormality (Table 3). There was a large variation in the rate of prenatal diagnosis, from 94% of cases with anencephalus to 27% of cases with transposition of the great arteries. Termination of pregnancy was performed in more than half of the prenatally diagnosed cases except for transposition of the great arteries, diaphragmatic hernia and gastroschisis, where 30–40% of the pregnancies with a prenatal diagnosis were terminated. For severe limb reduction defects, 56 of 101 (55%) cases were diagnosed prenatally and 43 (43%) cases were terminations of pregnancy.

Overall, 69% of the malformations were diagnosed before 24 weeks of gestation, 24% were diagnosed from 24 weeks or later, and for 7% the gestational age at discovery was unknown (Table 4). Only 7% of cases with anencephalus were diagnosed late (24 weeks or later) while more than one third of the cases with hydrocephalus, transposition of the great arteries and diaphragmatic hernia were diagnosed at 24 weeks or later.

Table 2 Gestational age (GA) at discovery for prenatally detected malformations in 17 European regions, 1995–1999*

Region	Cases diagnosed prenatally (n)	GA at discovery (n (%))			Terminations of pregnancy (n) (GA < 24 weeks/GA ≥ 24 weeks)	Median GA at discovery (weeks)
		< 24 weeks	≥ 24 weeks	Unknown		
Antwerp	99	57 (58)	20 (20)	22 (22)	50/3	19
Hainaut	127	79 (62)	33 (26)	15 (12)	58/11	20
Sofia	47	17 (36)	27 (57)	3 (6)	15/11	26
Croatia	13	5 (38)	6 (46)	2 (15)	5/2	24
Funen County	38	19 (50)	18 (47)	1 (3)	15/0	21
Paris	887	622 (70)	259 (29)	6 (1)	474/113	22
Strasbourg	213	160 (75)	51 (24)	2 (1)	130/28	20
Mainz	109	43 (39)	66 (61)	0	23/2	26
Saxony-Anhalt	109	73 (67)	16 (15)	20 (18)	64/9	19
Campania	263	186 (71)	42 (16)	35 (13)	171/13	20
Tuscany	145	81 (56)	17 (12)	47 (32)	68/3	19
Malta	36	15 (42)	21 (58)	0	—	27
South Portugal	74	37 (50)	21 (28)	16 (22)	25/1	21
Asturias	83	64 (77)	14 (17)	5 (6)	57/1	18
Basque Country	187	138 (74)	30 (16)	19 (10)	125/4	19
Vaud	92	68 (74)	22 (24)	2 (2)	60/5	19
Wales	284	250 (88)	28 (10)	6 (2)	178/6	19
Total	2806	1914 (68)	691 (25)	201 (7)	1518/212	20

*Bulgaria and Campania reported cases in 1996–1999 and Wales reported cases in 1998–1999.

Table 3 Prenatal diagnosis of 11 severe malformations and subsequent termination of pregnancy in 17 European regions, 1995–1999*

Malformation	Cases (n)	Cases with chromosomal anomaly (n (%))	Time of diagnosis known	Prenatal diagnosis (n (%))	Terminations of pregnancy (n (%))	Ratio terminations/prenatal diagnosis
Anencephalus	498	8 (2)	493	469 (94)	421 (85)	0.90
Encephalocele	162	10 (6)	159	128 (79)	107 (66)	0.84
Spina bifida	599	46 (8)	592	405 (68)	314 (52)	0.78
Hydrocephalus	816	77 (9)	792	626 (77)	393 (48)	0.63
Transposition of the great arteries	324	8 (2)	314	89 (27)	36 (11)	0.40
Hypoplastic left heart	289	32 (11)	282	164 (57)	113 (39)	0.69
Limb reduction defects	694	48 (7)	688	251 (36)	168 (24)	0.67
Bilateral renal agenesis	257	17 (7)	251	201 (78)	158 (61)	0.79
Diaphragmatic hernia	377	41 (11)	367	197 (52)	68 (18)	0.35
Omphalocele	355	99 (27)	344	275 (77)	176 (50)	0.64
Gastroschisis	196	5 (3)	196	175 (89)	53 (27)	0.30
Total malformations	4567	391 (9)	4478	2980 (65)	2007 (44)	0.67
Total cases	4366		4278	2806 (64)	1863 (43)	0.66

All percentages are of total number of cases. *Bulgaria and Campania reported cases in 1996–1999 and Wales reported cases in 1998–1999.

Among the late terminations (≥ 24 weeks) the majority of cases had hydrocephalus or spina bifida.

For live births, the median gestational age at birth was 37 weeks for cases with a prenatal diagnosis and 39 weeks for cases with a postnatal diagnosis. This difference was highly significant ($P < 0.001$).

DISCUSSION

Our data concern severe structural malformations potentially detectable by prenatal ultrasound. Down syndrome has been analyzed separately⁷. Our data show wide regional variation in the rate of prenatal diagnosis

of these malformations in Europe. We also found differences in the proportion of pregnancies terminated after prenatal diagnosis. Regional differences have also been reported from EUROCAT data for earlier time periods^{8,9} and for the group of registries taking part in the EUROSCAN study^{2,10–14}. The reasons for the differences in prenatal detection rate between regions cannot be clarified by this study, but they may be explained by different screening policies, differences in pregnant women's attitudes to screening, differences in technology and skills and differences in laws regarding the upper gestational age limit for terminations. Our study also showed a very clear relationship between

Table 4 Gestational age (GA) at discovery for prenatally detected malformations in 17 European regions, 1995–1999*

Malformation	Cases diagnosed prenatally (n)	GA at discovery (n (%))			Terminations of pregnancy (n) (GA < 24 weeks/GA ≥ 24 weeks)	Median GA at discovery (weeks)
		< 24 weeks	≥ 24 weeks	Unknown		
Anencephalus	469	394 (84)	34 (7)	41 (9)	366/18	16
Encephalocele	128	104 (81)	18 (14)	6 (5)	94/8	19
Spina bifida	405	278 (69)	107 (26)	20 (5)	253/44	21
Hydrocephalus	626	325 (52)	248 (40)	53 (8)	273/87	22
Transposition of great arteries	89	47 (53)	38 (43)	4 (4)	27/7	22
Hypoplastic left heart	164	102 (62)	51 (31)	11 (7)	87/19	22
Limb reduction defects	251	183 (73)	56 (22)	12 (5)	147/14	20
Bilateral renal agenesis	201	149 (74)	34 (17)	18 (9)	134/11	21
Diaphragmatic hernia	197	108 (55)	77 (39)	12 (6)	57/8	23
Omphalocele	275	223 (81)	29 (11)	23 (8)	156/6	17
Gastroschisis	175	138 (79)	26 (15)	11 (6)	45/1	18
Total	2980	2051 (69)	718 (24)	211 (7)		

All percentages are of total number of cases. *Bulgaria and Campania reported cases in 1996–1999 and Wales reported cases in 1998–1999.

high prenatal detection rate and early prenatal diagnosis. Furthermore, with early diagnosis more pregnancies were terminated.

The data on terminations of pregnancy per 1000 births indicate the potential impact of prenatal diagnosis and terminations of pregnancy on perinatal mortality. Not all terminations of pregnancy with the malformations included in this study would have contributed to perinatal mortality if the pregnancy had continued. If we assume that all terminations with anencephalus and bilateral renal agenesis and half of the other terminations in this study would have contributed to perinatal mortality if they had not been terminated, there would have been an additional 1221 cases, increasing perinatal mortality by 1.02 per 1000 births. This rate should be compared to the published data on perinatal mortality in Europe, which is as low as 5.4 per 1000 births in Sweden and Finland¹⁵ and 5.6 in Germany¹⁶.

There was some variation in prevalence of the 11 malformations between registries, but the majority of regions had a prevalence of between 3 and 5 per 1000 births. The case definition of hydrocephalus may differ between regions and prevalence varies from 1.6 to 22.2 per 10 000 births¹⁷. The lowest rates are likely to be due to underdiagnosis or underascertainment of cases and the highest reported prevalence may be caused by inclusion of cases with only small dilatation of the ventricles. The proportion of cases with hydrocephalus varies between registries from 9% of the cases included (Croatia) to 25% (Mainz and Paris)¹⁷. Therefore, differences in the number of included cases with hydrocephalus may explain a considerable proportion of the variation in prevalence.

For anencephalus and bilateral renal agenesis survival is not possible and for these two malformations the prenatal detection rates and the rates of termination of pregnancy after prenatal diagnosis were very high. For infants with transposition of the great arteries, diaphragmatic hernia and gastroschisis, surgery in the

neonatal period is necessary for survival, but long-term outcome is reported to be favorable if the infant survives the surgery and the following intensive care^{5,18–20}. For these cases the advantage of prenatal diagnosis will be the possibility of referral to a specialist center for birth and neonatal surgery. Our data show that a third of the pregnancies diagnosed prenatally with one of these three malformations are terminated compared with more than two thirds of the pregnancies diagnosed prenatally with the other eight malformations included in this study. We can conclude that the long-term prognosis of the malformed fetus has a major impact on the decision taken by the parents concerning termination of pregnancy. This was also the conclusion of a previous study that interviewed the mothers²¹. More information on the long-term prognosis for infants with congenital malformations is therefore important for counseling the parents after prenatal detection of a malformation.

Three malformations (hydrocephalus, hypoplastic left heart and diaphragmatic hernia) may not be present at the usual time of ultrasound screening (16–18 weeks) but may evolve later in pregnancy. For these three malformations the gestational age at discovery was later than that for the other malformations included in this study, with the exception of transposition of the great arteries. Transposition of the great arteries may be difficult to diagnose during the ultrasound screening procedure as the transposed arteries are seen only by visualizing the outflow tracts of the heart and cannot be seen in the four-chamber view. These difficulties may explain the rather low prenatal detection rate.

Our study showed a significant difference in gestational age at birth for liveborn cases diagnosed prenatally and postnatally. With a median gestational age at birth of 37 weeks for prenatally diagnosed cases, half of all the cases were delivered preterm. It is possible that the knowledge of a malformation makes the obstetricians more inclined to induce the birth. It is important for these liveborn cases with severe malformations not to

increase their morbidity further by adding the risk of preterm birth. However, differences in severity may also be a partial explanation of the data, and the liveborn prenatally diagnosed cases may include some cases where survival was not possible, and where birth was induced shortly after the prenatal diagnosis.

European countries currently vary widely in the provision and uptake of prenatal screening and its quality, as well as in their 'culture' in terms of decision to carry on the pregnancy. This inevitably contributes to variation between countries in perinatal and infant mortality and in childhood prevalence and cost to health services of congenital anomalies.

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