The epidemiology of tracheo-oesophageal fistula and oesophageal atresia in Europe

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Abstract

The total prevalence rate of tracheo-oesophageal fistula and oesophageal atresia in 15 EUROCAT registries covering 1 546 889 births during 1980-8 was 2.86 per 10 000. There was a decreasing prevalence rate over time (3.5 per 10 000 in 1980-2, 2.7 in 1983-5, 2.5 in 1986-8). Ten per cent of cases were associated with chromosomal anomalies and of the remaining cases, half were multiply malformed. Sixty two per cent of cases were males. There was a significantly increased risk for mothers of less than 20 years of age (odds ratio compared with mothers of 25-29=1.82, 95% confidence interval 1.23 to 2.67). There were no apparent epidemiological differences between isolated and multiply malformed cases in secular trend, sex ratio, or maternal age. Both isolated and multiply malformed cases tended to be premature and small for gestational age. There was variation between centres in survival of affected liveborn children up to 1 year of age.

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Tracheo-oesophageal fistula and oesophageal atresia (TOFA) is a group of congenital anomalies occurring by the sixth week of embryonic life.¹ Most forms are well recognised at birth through their symptomatology and may be suspected prenatally because of maternal polyhydramnios.

There are various reports indicating environmental and/or genetic factors in the aetiology of the malformation,¹⁻⁴ and probable aetiological heterogeneity of the condition. There is a need for more epidemiological data to clarify these issues and to form a background for analytic studies.

EUROCAT is a concerted action of the European Community for the surveillance of congenital anomalies. Regional registries cover geographically defined populations in Europe. This descriptive registry based study aims to provide an epidemiological overview of TOFA in Europe for a recent time period (1980-8). Although more than 1.5 million births were surveyed in the time period considered, this is nevertheless not sufficient for a detailed analysis of some variables of interest, such as twins, siblings, and individual associated malforma-

tions. The study has therefore been carried out in collaboration with the International Clearing-house,⁵ so that these data can be pooled with those of other surveillance systems.

Methods

The study population consisted of a total of 1 546 889 births surveyed by 15 registries 1980-8 (table 1). The populations covered and the registration system in each of the EUROCAT registries have been described in previous publications.^{6,7} In nine centres (Florence, Dublin, Galway, Groningen, Glasgow, Northern Ireland, Liverpool, Marseille, and Malta) the registration system covers all births to mothers resident in a geographically defined area. In three centres (Hainaut, West Flanders, and Zagreb) the reference population consisted of all births occurring in all the maternity units of a defined geographical area. In Paris and Strasbourg, all births in all maternity units of a geographical area were surveyed, but in Paris births from outside Greater Paris were excluded from both numerator and denominator, and in Strasbourg all referrals specifically for malformation from outside the region were excluded. The Luxembourg registry covered 55% of births in the country; the other 45% took place in a single non-participating maternity unit.

Most registries covered a population of stable size, except Groningen which expanded its area in 1986 from an annual 7800 births to nearly 12 000, and Zagreb that expanded from 4000 annual births 1983-5 to nearly 7000 in 1986.

Ascertainment of congenital anomalies was based on the use of multiple sources of information such as birth and death certificates, maternity and hospital records, and cytogenetic and pathology service reports. The use of these various sources differed from registry to registry.

Table 1 Total prevalence rate per 10 000 by centre, 15 EUROCAT registries

Centre	Total births	Years covered	Total cases	Rate/10 000
West Flanders	68 228	1980-8	21	3.08
Hainaut	74 675	1980-8	28	3.75
Paris	287 022	1981-8	70	2.44
Florence	80 660	1980-8	22	2.73
Dublin	204 204	1980-8	68	3.33
Galway	22 344	1981-7	7	3.13
Luxembourg	22 024	1980-8	4	1.82
Groningen	73 879	1981-8	22	2.98
Glasgow	117 323	1980-8	38	3.24
Liverpool	163 613	1980-7	50	3.06
Belfast	223 048	1980-7	62	2.78
Strasbourg	91 869	1982-8	24	2.61
Zagreb	31 572	1983-8	7	2.22
Marseille	70 281	1985-7	14	1.99
Malta	16 147	1986-8	5	3.10
All centres	1 546 889		442	2.86

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Table 2 Number of all cases of TOFA and rate per 10 000 over three time periods, 15 EUROCAT registries

Years	West Flanders		Hainaut		Paris		Florence		Dublin		Galway		Luxembourg		Groningen	
	No	Rate	No	Rate	No	Rate	No	Rate	No	Rate	No	Rate	No	Rate	No	Rate
1980-2	12	6.08	14	5.63	15	2.15	9	3.18	30	3.94	3	4.52	0	0.00	5	3.20
1983-5	4	1.77	7	2.90	32	2.96	9	3.38	21	3.16	2	2.11	1	1.42	5	2.18
1986-8	5	1.93	7	2.72	23	2.11	4	1.56	17	2.76	2	3.22	3	3.77	12	3.39
All years	21	3.08	28	3.75	70	2.44	22	2.73	68	3.33	7	3.13	4	1.82	22	2.98

Livebirths, fetal deaths, and induced abortions for congenital anomaly were registered. Stillbirths may include fetal deaths of 20 weeks' gestational age or more, but registries may have more systematic access to information on fetal deaths classified as stillbirths in their region according to other gestational or birthweight criteria (180 days, 28 weeks, 500 g, etc). Induced abortions during the study period had an upper gestational age limit of 27 weeks except in France where there was no upper limit.

Induced abortions are illegal in Ireland and Malta. They were illegal but tolerated in cases of severe malformation in Northern Ireland and Belgium. In West Flanders, Zagreb, and Luxembourg there was no information available to the registry on cases of congenital anomaly that had been prenatally diagnosed and aborted but which otherwise would have formed part of the study populations.

Maximum age at registration varied between the centres. Centres where more than 10% of all congenital anomalies registered during the study period were first detected after one month of age are Strasbourg, Groningen, Glasgow, and Liverpool.

Congenital anomalies were coded according to the International Classification of Diseases (ICD)/British Paediatric Association system.^{8,9} Oesophageal atresia and tracheo-oesophageal fistula included any codes where the first four digits were 7503.

Infants with at least one other major malformation, apart from the TOFA anomaly, were defined as multiply malformed. Infants without a further malformation were defined as 'isolated cases'. Anomalies that were not considered major congenital anomalies include sacral dimple, patent ductus arteriosus in premature or low birthweight babies, single umbilical artery, hiatus hernia, abnormal palmar creases, congenital ptosis, preauricular appendage, macrotia, bat ear, misplaced ear, cardiomegaly, pharyngeal pouch, high arched palate, pyloric stenosis, Meckel's diverticulum, undescended testicle, ectopic testis, and clicking hip.

Infants with a chromosomal anomaly (ICD 758) were analysed as a separate category to isolated and multiply malformed cases. For the two most common chromosomal syndromes, Down's syndrome and Edward's syndrome, reference was also made to the entire registration data for the same population and period.

The birth weight for gestational standard used was that of Yudkin *et al*¹⁰ because appropriate comparison statistics were not available from the source populations. Birth weight and gestational age were analysed excluding induced abortions.

Maternal age denominators were available from population statistics. These statistics were

incomplete for West Flanders (1981-4 only), Hainaut (1981-4 only), and Florence (1981-2 only). Maternal age was analysed excluding chromosomal anomalies among cases.

Centres were invited to supplement or verify the routine records for information on survival, type of TOFA, and anomalies in siblings. Six centres (Paris, Dublin, Groningen, Glasgow, Marseille, and Malta) provided supplementary information, and analysis of these variables was restricted to these centres.

In calculating the total number of previous siblings, the 14% of cases with unknown maternal parity were assigned the average parity of the centre concerned.

A total prevalence rate was defined as the total number of cases in livebirths, stillbirths, and induced abortions after prenatal diagnosis of malformation, divided by the total number of births in the population.

The χ^2 test for homogeneity in proportions was used to test whether differences in total prevalence rates were significant between regions or over time and whether ratios (isolated to multiply malformed, or male to female) varied between regions. Centres too small to reach the requirement of an expected number of at least five cases in χ^2 analyses were excluded, and these exclusions can be seen by the number of degrees of freedom in the analysis. To test for secular trend the χ^2 test for homogeneity was subdivided into a component that tests for linear trend and a component that tests for departures from linearity. Confidence intervals (CI) for odds ratios and Mantel-Haenszel stratification for odds ratios were calculated where indicated by using the Epi Info statistical package.

Results

PREVALENCE

A total of 442 cases were recorded, giving a prevalence rate of 2.86 per 10 000 births (table 1). The prevalence rate did not vary significantly between the 15 regions ($\chi^2=9.9$, 14 df, $p>0.05$). The proportion of livebirths was 89.6%, stillbirths 6.6%, and induced abortions 3.6%.

The total prevalence rate decreased over the time period considered: 3.50 per 10 000 in 1980-2, 2.70 per 10 000 in 1983-5, and 2.50 per 10 000 in 1986-8 (χ^2 for trend=8.3, 1 df, $p<0.01$, χ^2 for trend stratified by registry=6.2, $p<0.05$). The extent to which this overall decrease is mirrored in individual registries can be seen in table 2.

Overall, 1.8% of cases were recorded as first suspected after 1 month of age, coming from Groningen (n=1), Dublin (n=2), Belfast (n=1), Strasbourg (n=1), Glasgow (n=1), Florence (n=1), and Paris (n=1).

Glasgow		Liverpool		Belfast		Strasbourg		Zagreb		Marseille		Malta		All cases	Total births	Total rate
No	Rate	No	Rate	No	Rate	No	Rate	No	Rate	No	Rate	No	Rate			
16	4.02	14	2.29	32	3.83	6	4.39	—	—	—	—	—	—	156	446 194	3.50
11	2.85	18	2.94	20	2.41	12	3.11	2	1.69	3	1.28	—	—	147	544 178	2.70
11	2.82	18	4.36	10	1.78	6	1.52	5	2.53	11	2.35	5	3.10	139	556 517	2.50
38	3.24	50	3.06	62	2.78	24	2.61	7	2.22	14	1.99	5	3.10	442	1 546 889	2.86

ASSOCIATED MALFORMATIONS

Ten per cent of cases were associated with a chromosomal anomaly (22 with Down's syndrome or 1% of all Down's syndrome cases registered during the same period, 21 with trisomy 18 or 6.3% of all trisomy 18 cases, and one partial trisomy 13). The karyotype was known to the registry in 75% of these chromosomal cases. Sixteen per cent of the chromosomal cases were induced abortions and 9% stillbirths.

Of the remaining 398 cases, exactly half were isolated TOFA malformations and half had other major associated malformations. The ratio of isolated to multiply malformed cases did not vary significantly between registries ($\chi^2=13.7$, 10 df, $p>0.05$). Two per cent of the isolated cases and 23% of the multiply malformed cases were confirmed to be non-chromosomal with a karyotype.

The proportion of stillbirths was 2.5% for isolated cases and 10.1% for multiply malformed cases.

Associated anomalies included cardiac anomalies in 17.1% of non-chromosomal cases (and 50% of chromosomal cases) and anorectal atresia or stenosis in 11.6% of non-chromosomal cases (0% of chromosomal).

The downward trend in prevalence was examined for isolated and multiply malformed cases separately. For isolated cases the total prevalence rate was 1.46 per 10 000 in 1980–2, 1.16 per 10 000 in 1983–5, and 1.28 per 10 000 in 1986–8, with no statistically significant variation between time periods. For multiply malformed cases the rates were 1.66, 1.27, and 1.01 per 10 000 for the respective time periods, with a significant downward trend ($\chi^2=8.1$, 1 df, $p<0.01$). Nevertheless, the ratio of isolated to multiply malformed cases did not vary significantly or show a statistically significant trend across the three time periods (the ratio was 0.88 in 1980–2, 0.91 in 1983–5, and 1.26 in 1986–8).

TYPE OF ANOMALY

Oesophageal stenosis was recorded in 15 of the 442 cases (two in West Flanders, three in Hainaut, one in Paris, two in Dublin, one in Groningen, one in Glasgow, one in Liverpool, three in Belfast and one in Strasbourg). Nine of these cases were isolated malformations. None was associated with a chromosomal anomaly. Two cases had been detected after 1 month of age and it is likely that other late diagnosed cases may not have been registered.

An inquiry made in six centres (Paris, Dublin, Groningen, Glasgow, Marseille, and Malta) found the following distribution of anomaly types among the 217 cases: 16% unknown types, 4% absence of atresia of oesophagus without

fistula, 67% absence or atresia of oesophagus with fistula, 9% fistula without atresia, and 3% other (one broncho-oesophageal fistula with oesophageal atresia and one without oesophageal atresia and five cases of stenosis of oesophagus).

Among the cases of fistulas without atresia the majority were multiply malformed cases rather than isolated (13 multiply malformed and four isolated). In comparison among the cases of atresia with fistula there was a slight majority of isolated cases (58 multiply malformed and 78 isolated).

SEX RATIO

Sixty two per cent of all isolated cases were males (95% CI 55 to 69%), and 61% of all multiply malformed cases (95% CI 54 to 68%). These proportions did not vary significantly between regions. Fifty seven per cent of chromosomal cases were males (95% CI 42 to 71%).

MATERNAL AGE

Total prevalence rates by maternal age group are shown in table 3. An increased risk is seen for both young (<20 years) and older (35+) mothers, but the increased risk for older mothers is explained by the inclusion of chromosomal cases.

Excluding chromosomal cases, and comparing all maternal age-specific rates with the 25–29 age group, there is a statistically significant increased risk only for the young mothers <20 years (odds ratio=1.82, 95% CI 1.23 to 2.67, Mantel-Haenszel odds ratio stratified by registry=1.69, 95% CI 1.13 to 2.49).

A similar pattern of maternal age-specific risk is seen for both isolated and associated cases (table 3). The difference in odds ratios for young mothers was not statistically significant ($\chi^2=0.11$, $p>0.05$).

TWINS

There were a total of 18 twins (4.1% of all cases, 95% CI 2.3 to 6.1%). Ten cases had an isolated malformation (5.0% of all isolated cases), and five were multiply malformed (2.5% of multiply malformed cases), but the difference between these proportions is not statistically significant. Three twins had chromosomal anomalies (6.8% of all chromosomal cases). These proportions should be compared with the approximately 2 to 2.2% of births in the EUROCAT populations that are twins or multiple births.

One twin pair was concordant for TOFA and Down's syndrome. In this pair there was discordance for presence of a fistula. One monozygotic twin who was multiply malformed

Table 3 Total prevalence rate per 10 000 by maternal age group, 15 EUROCAT registries

	Maternal age group				
	<20	20-24	25-29	30-34	35+
All cases					
No	38	97	138	96	60
Rate	4.3	2.4	2.5	2.8	3.7
All cases excluding chromosomal					
No	36	91	124	89	44
Rate	4.1	2.3	2.3	2.6	2.7
Isolated					
No	16	48	59	44	22
Rate	1.8	1.2	1.1	1.3	1.4
Associated					
No	20	43	65	45	22
Rate	2.3	1.1	1.2	1.3	1.4

(including cardiac anomalies, genitourinary anomalies, and phocomelia) had a co-twin with bifid thumb and single umbilical artery. All other co-twins were normal.

FAMILIAL RECURRENCE

Analysis of previous siblings with anomalies was restricted to six centres that could supply confirmed information. Whether a previous sibling was malformed was known in 98% of cases. Chromosomal cases were excluded from analysis.

Three cases had a sibling with TOFA. In one sibling pair, the first sibling also had duodenal atresia, and the second also had bilateral dilatation of the renal pelvis. In the second pair, the first sibling also had cleft lip, and the second sibling also had tetralogy of Fallot, cleft lip with cleft palate, and single umbilical artery. In the third pair, the first sibling also had a cardiopathy, but the second sibling had an isolated TOFA.

These centres covered between them 262 previous pregnancies (live and stillbirths) for the cases where information about siblings was known. The precurrence rate thus calculated is one in 87.

Other anomalies in siblings in the six centres were atresia of bile ducts ($n=1$), vesicoureteric reflux ($n=1$), unspecified renal anomaly ($n=1$), unspecified congenital heart disease ($n=2$), congenital dislocation of hip ($n=1$), transposition of great vessels ($n=1$), and shortened femur ($n=1$). A total of eight cases among 262 previous pregnancies gives a precurrence rate for other anomalies of 3.1%, not significantly higher than the general malformation rates in the six populations, ranging from 1.8 to 3.2%.⁷

In the remaining nine centres there were 112 previous pregnancies where information about siblings was recorded as known. There were no precurrences among these cases. Other anomalies in four siblings were: trisomy 21 ($n=1$), anencephaly ($n=1$), and unspecified ($n=2$).

Information about parents is routinely requested on case report forms, but no parents were reported to be affected by TOFA.

BIRTH WEIGHT AND GESTATIONAL AGE

Table 4 shows the high proportion of cases with low or very low birth weight (40% of isolated cases and 62% of multiply malformed cases). As

might be expected, birth weight was lower among the multiply malformed cases.

There was also a high rate of prematurity: 28% of isolated cases and 48% of multiply malformed cases were premature births (table 4). Both isolated and multiply malformed cases tend to be small for gestational age (table 4). Thirty one per cent of isolated cases and 49% of multiply malformed cases had a birth weight less than the tenth centile for gestational age.

SURVIVAL

Survival up to 1 year of age was investigated in four registries as shown in table 5. Survival rates were high for isolated cases in Dublin (93.5%) and Groningen (100.0%) but lower in Glasgow (64.3%). For multiply malformed cases, survival was generally lower (51.7% in Dublin, 50.0% in Groningen, and 17.6% in Glasgow). In Malta, there were four isolated cases all surviving to 1 year, and a chromosomal case lost to follow up after livebirth.

PRENATAL DIAGNOSIS AND INDUCED ABORTION

In four centres (Hainaut, Paris, Marseille, and Glasgow) 10 isolated cases were prenatally diagnosed where the outcome of pregnancy was a livebirth, 14.5% of all isolated cases in these centres.

All 16 induced abortions after prenatal diagnosis were multiply malformed ($n=9$) or chromosomal ($n=7$) cases, from five centres (Groningen, Glasgow, Hainaut, Paris, and Marseille). A further 24 multiply malformed cases and six chromosomal cases were prenatally diagnosed where the outcome of pregnancy was a livebirth or stillbirth in these five centres as well as Liverpool, Belfast, Strasbourg, Galway, and Dublin.

Discussion

The prevalence rate of TOFA reported here is similar in different regions of Europe, and is broadly similar to rates quoted in the literature from within and outside Europe^{2,3,11} although a higher rate of 4.1 per 10 000 has been reported in Finland.⁴

The downward trend in prevalence over time, which requires further investigation, raises the possibility of an environmental factor that is

Table 4 Low birth weight and prematurity among isolated and multiply malformed cases; results are number (%)

	Isolated	Multiply malformed
Birth weight (g)*		
<1500	6 (6.8)	19 (18.5)
1500-2499	31 (33.0)	21 (43.9)
Gestational age (weeks)†		
<32	14 (8.6)	24 (15.0)
33-36	32 (19.6)	53 (33.4)
Weight for gestational age <10th centile (weeks)‡		
28-32	2 (16.7)	9 (36.0)
33-36	10 (32.3)	35 (58.3)
37+	35 (32.1)	43 (47.3)

*Excluding Marseille; †excluding Dublin; ‡excluding Dublin and Marseille.

All exclusions made due to high proportion of missing values.

Table 5 Survival to 1 year of age, four EUROCAT registries

	Total cases	No (%) stillbirths	No (%) livebirths			Survivors at 1 year	
			Died <7 days	Died 7 days-1 month	Died 1 month-1 year	% Total	% Livebirths
All cases							
Dublin*	68	7 (10.3)	8 (11.8)	3 (4.4)	2 (2.9)	70.1	78.3
Groningen	19	2 (10.5)	4 (21.1)	3 (15.8)	0	52.6	58.8
Glasgow	35	1 (2.9)	11 (31.4)	8 (22.9)	3 (8.6)	34.3	35.3
Malta*	5	0	0	0	0	100.0	100.0
Isolated cases							
Dublin	31	1 (3.2)	1 (3.2)	0	0	93.5	96.8
Groningen	5	0	0	0	0	100.0	100.0
Glasgow	14	1 (7.1)	1 (7.1)	2 (14.3)	1 (7.1)	64.3	69.2
Malta	4	0	0	0	0	100.0	100.0
Multiply malformed cases							
Dublin*	29	6 (20.7)	6 (20.7)	2 (6.9)	0	51.7	65.2
Groningen	10	2 (20.0)	2 (20.0)	1 (10.0)	0	50.0	62.5
Glasgow	17	0	8 (47.1)	5 (29.4)	1 (5.9)	17.6	17.6

*One livebirth was lost to follow up.

changing over time. This factor seems to be widespread as the decrease is found in a number of widely spread regions. Time and time space clusters of TOFA have been reported,^{4 11 12} and an infective origin suggested.

There is a small excess of males among cases (62% of cases). Other studies have reported either a small or no excess of males.^{3 13}

Ten per cent of this case series were associated with chromosomal anomalies (Down's syndrome or trisomy 18). The large proportion of these cases that were stillbirths or induced abortions (25%) may explain to some extent why more chromosomal cases were reported here than in series based on livebirths,^{3 11 14} although lower proportions in other studies may also be due to lack of karyotype confirmation of cases.¹³ In the present series also, some chromosomal anomalies may not have been diagnosed as the proportion of karyotypes among other cases was low. However, the lack of increased risk for non-chromosomal cases in the older maternal age group suggests that there was little misclassification.

The proportion of multiply malformed cases in the present series is in the upper part of the range of 30–57% (including chromosomal anomalies) reported elsewhere.^{13 11 14} Lower proportions can be expected in series based on livebirths only.

It is of interest to consider whether multiply malformed cases (excluding chromosomal cases) differ aetiologically from isolated cases. We could find no direct differences between the two groups in secular decline, sex ratio, or maternal age. One of the three affected sibling pairs was discordant for the presence of another major anomaly (a cardiac anomaly). However, there was a slight though non-significant suggestion of a higher proportion of twins among isolated cases. Nevertheless, the grouping of all multiply malformed cases together is probably quite insensitive, and a larger case series is needed to look at specific associations between anomalies, considering further also the VATER association.¹⁵

An analysis of different types of TOFA was limited in this series by the lack of detailed case description in most centres. As is generally observed, the vast majority of cases had oesophageal atresia with tracheo-oesophageal fistula.^{12 14}

The proportion of fistulas without atresia (over 9%) is higher than that reported in the literature.¹¹³ The higher proportion of multiply malformed cases among those with fistulas without atresia in this series might be to some extent explained by delayed detection of this anomaly when it is in an isolated form¹¹⁶ and therefore underascertainment of isolated cases.

A higher rate of TOFA could be demonstrated among younger mothers of less than 20 years of age. In an English study where maternal age was analysed,¹³ both young (<20) and older (>35) mothers were shown to have an increased risk. The results of the present study suggest that any increase shown among older mothers is attributable to chromosomal abnormalities.

The precurrence rate among siblings estimated here (3/262) was greater than that reported in a previous study where only one in 340 previous siblings was affected by TOFA.¹³ As familial cases seem to be rare, large series will be needed for analysis. The lack of concordant twins among non-chromosomal cases and the very low precurrence rate in siblings supports the importance of non-genetic factors in the aetiology of the anomaly.

No parents were found to be affected. Although there may have been cases where the anomaly in a parent was not reported, this suggests that survival of infants with TOFA to reproductive age since the introduction of effective surgery is not causing any unexpected increase in familial cases.

The higher than expected rate of twinning among TOFA cases suggests that twinning may predispose towards these malformations or that common aetiological factors are involved. Differences in the proportion of twins between isolated, multiply malformed, and chromosomal cases need confirmation in a larger data set before it is possible to speculate further on their significance.

Treatment of TOFA is generally successful and survival depends on the presence of other associated major anomalies. The apparently lower survival of both isolated and multiply malformed cases in Glasgow is being investigated by the local paediatric surgeons, who have expressed their concern at the findings. In a comparison between centres, stillbirths and very early postnatal deaths should be grouped together, but Glasgow continued with a low survival rate after 1 week of age.

Poor fetal growth and prematurity seem to be characteristics of TOFA, whether isolated or associated with other major malformations. As it cannot be said whether poor growth predisposes to, is a consequence of, or is simply associated with the malformation, it is not clear whether population measures preventing prematurity or fetal growth retardation will have any effect on the incidence of the malformation. The generally improving survival rates for very low birth-weight infants may be expected to lead to a slight increase in TOFA prevalence among livebirths.

The higher than expected proportion of stillbirths among isolated cases points to a common cause of reduced fetal survival and the malformation, a factor which may also be implicated in poor fetal growth. However, the possibility that

fetal death was associated with undiagnosed internal malformations cannot be excluded.

TOFA constitutes an ideal subject for collaborative investigation, being relatively easily diagnosed and classified in a standard fashion, and recognised soon after birth. As enormous progress has been made in the treatment of this condition, the next significant development will come from aetiological research leading to primary prevention.

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