

# Evaluation of prenatal diagnosis of associated congenital heart diseases by fetal ultrasonographic examination in Europe

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Ultrasound scans in the mid trimester of pregnancy are now a routine part of antenatal care in most European countries. With the assistance of Registries of Congenital Anomalies a study was undertaken in Europe. The objective of the study was to evaluate prenatal detection of congenital heart defects (CHD) by routine ultrasonographic examination of the fetus. All congenital malformations suspected prenatally and all congenital malformations, including chromosome anomalies, confirmed at birth were identified from the Congenital Malformation Registers, including 20 registers from the following European countries: Austria, Croatia, Denmark, France, Germany, Italy, Lithuania, Spain, Switzerland, The Netherlands, UK and Ukraine. These registries follow the same methodology. The study period was 1996–1998, 709 030 births were covered, and 8126 cases with congenital malformations were registered. If more than one cardiac malformation was present the case was coded as complex cardiac malformation. CHD were subdivided into 'isolated' when only a cardiac malformation was present and 'associated' when at least one other major extra cardiac malformation was present. The associated CHD were subdivided into chromosomal, syndromic non-chromosomal and multiple. The study comprised 761 associated CHD including 282 cases with multiple malformations, 375 cases with chromosomal anomalies and 104 cases with non-chromosomal syndromes. The proportion of prenatal diagnosis of associated CHD varied in relation to the ultrasound screening policies from 17.9% in countries without routine screening (The Netherlands and Denmark) to 46.0% in countries with only one routine fetal scan and 55.6% in countries with two or three routine fetal scans. The prenatal detection rate of chromosomal anomalies was 40.3% (151/375 cases). This rate for recognized syndromes and multiply malformed with CHD was 51.9% (54/104 cases) and 48.6% (137/282 cases), respectively; 150/229 Down syndrome (65.8%) were livebirths. Concerning the syndromic cases, the detection rate of deletion 22q11, situs anomalies and VATER association was 44.4%, 64.7% and 46.6%, respectively. In conclusion, the present study shows large regional variations in the prenatal detection rate of CHD with the highest rates in European regions with three screening scans. Prenatal diagnosis of CHD is significantly higher if associated malformations are present. Cardiac defects affecting the size of the ventricles have the highest detection rate. Mean gestational age at discovery was 20–24 weeks for the majority of associated cardiac defects. Copyright © 2001 John Wiley & Sons, Ltd.

**KEY WORDS:** birth defects; congenital malformations; congenital anomalies; congenital heart diseases; congenital heart defects; prenatal diagnosis; ultrasound screening

## INTRODUCTION

Fetal ultrasound examination for detection of congenital malformations is now part of antenatal care in

most European countries. As technology and operator skill improve more fetal malformations are recognised by the scan (Sollie *et al.*, 1988; Sharland and Allan, 1992; Grandjean *et al.*, 1999). What is possible is not, however, always practical in everyday practice, particularly when whole antenatal populations are screened rather than high-risk groups at referral centres (Constantine and McCormack, 1991). There are many reports of prenatal detection of malformation in high-risk groups but few studies have been reported on the effectiveness of anomaly detection by routine ultrasound scans, particularly for cardiac anomalies. Major cardiac malformations can be prenatally diagnosed but general screening of low-risk populations show a low detection rate from 14% to 45% (Boyd *et al.*, 1998; Hafner *et al.*, 1998; Stoll *et al.*, 1998; Klein *et al.*, 1999). However, when fetal cardiac screening is performed by detailed echocardiography detection rate is almost complete (Stümpflen *et al.*, 1996).

A European multicentre study was started in 1996.

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The aim of this study was to evaluate prenatal detection of congenital malformations by fetal ultrasonographic examination across Europe and to verify if there is homogeneity of expertise among the various centres. Prenatal diagnosis of isolated cardiac malformations was reported previously (Garne *et al.*, in press). The present report presents the results for associated cardiac malformation.

## DATA AND METHODS

Data were provided by 20 Registries of Congenital Malformations from 12 European countries using the same epidemiological methodologies; their general characteristics have been described previously (EUROCAT, 1997). Briefly, the registries were population-based, they had multiple sources of information for complete and accurate notification, ascertainment was active, and the denominators were well known. The scanning was performed routinely by trained operators in hospitals and in obstetricians' offices on all pregnant women. All malformations prenatally suspected were referred for confirmation to a specialized echographic centre. Patients underwent a detailed structural evaluation of the fetus.

Routine prenatal ultrasound screening for congenital malformations was performed in all registry areas except in the Danish and in The Netherlands registries. In countries in which more than one ultrasound scan is offered (Table 1), the scan performed in the first and/or third trimester of pregnancy was mainly for biometric purposes. Termination of pregnancy (TOP) after prenatal diagnosis of major congenital malformations was permitted in all registry areas.

All livebirths, stillbirths and TOP with a major malformation defined as a structural abnormality

detectable by ultrasound, diagnosed prenatally or within the first 7 days of life were included in the present study.

The registration form is completed by a member of the medical staff and contains information regarding time of diagnosis, the suspected and confirmed prenatal diagnosis, details of the mother, the pregnancy and the final pregnancy outcome. The coding system used by all participating registries for diagnosis was ICD/BPA 9 (British Paediatrics Association, 1979). All forms including a diagnosis on the list of inclusion for the study were transferred to a database (MS Access, Windows environment) for the analysis. The validation was performed at local and at central database level. Protection of privacy was assured, therefore confidentiality is preserved.

Diagnosis for inclusion in the cardiac subgroup were the ICD/BPA coding numbers 745.00–747.49 excluding cases with patent ductus as the only cardiac diagnosis. The cardiac malformations were divided into isolated when only a cardiac malformation was present and associated when at least one other major extra cardiac malformation was present. The associated cardiac anomalies were subdivided into chromosomal when associated with chromosomal anomaly, syndromic when cardiac malformation was part of a non-chromosomal malformation recognized syndrome, and multiple when not chromosomal and not syndromic. When more than one cardiac malformation was present in the same baby, the congenital heart defect (CHD) was considered as complex.

The study period was 1 July 1996 to 31 December 1998, however not all registries covered the whole time period. The total number of births in the registry areas was 709 030. The list of participating registries with the study period, the number of births and the number of cases are given in Table 2.

Table 1—Current practice regarding routine prenatal ultrasound screening for congenital malformations

<b>Ultrasonographic examination</b>	
One examination	
18–22 weeks	Oxford, Wessex, UK
Two examinations	
E, 20–22 weeks	Lausanne
L, 16–20 weeks	Styria, SW Ukraine
E, 16–18 weeks	Lithuania
Three examinations	
E, L, 18–22 weeks	Sicily, Tuscany, NE Italy, Mainz, Leipzig, El Valles
E, L, 18–20 weeks	Basque Country, Barcelona, Croatia
E, L, 18–24 weeks	Strasbourg, Paris
Not routine	Odense, The Netherlands: 80–90% have one examination
<b>Termination of pregnancy (TOP)</b>	
Possible anytime	France, Germany
≤22–24 weeks	Basque, Lithuania, Croatia, El Valles, Italy, Odense, Netherlands, Lausanne, Styria, UK
<28 weeks	SW Ukraine

E, Early, around 10 weeks' gestation, for biometric purposes.  
L, Late, around 30 weeks' gestation, for biometric purposes.

## Statistical methods

Descriptive data are presented as percentages or means  $\pm$  1 SD. Comparisons were performed using Chi-square and *t*-test statistics.

## RESULTS

As can be seen in Table 2, there were 761 cases of associated cardiac malformations including 375 cases with chromosomal anomalies, 104 syndromic cases and 282 cases with multiple non-chromosomal and non-syndromic cases. The prenatal detection rate is shown in Table 3 including the prenatal detection rate and the TOP before 24 gestational weeks. A total of 502 (65.9%) of the cases were livebirths, 45 (5.9%) were fetal deaths and 214 (28.1%) were TOP. Prenatal detection rate was 45.0%; 213 cases were diagnosed before 24 gestational weeks (27.9%) and 136 of these were terminated (17.9%).

There were large regional variations in prenatal detection of associated cardiac malformations (Table 3). The highest rate was in the European

Table 2—Associated congenital heart defects: registries participating in this study with the study period in months, the number of births and of malformed children with chromosomal, syndromic and multiple malformations

Registry	Study period (months)	Births ( <i>n</i> )	Associated number of cases			
			Total	Chromosomal	Syndromic	Multiple
Odense, Denmark	18	8788	13	8	2	3
Paris, France	9	27 550	78	39	16	23
Groningen, N Netherlands	30	34 085	32	16	2	14
Strasbourg, France	30	33 155	45	22	6	16
Lausanne, Switzerland	30	18 907	40	15	9	6
Croatia	30	10 718	7	3	1	3
NE Italy	30	111 719	87	40	10	37
Basque Country, Spain	24	32 429	46	23	7	7
Rotterdam, SW Netherlands	18	47 895	22	13	2	7
Mainz, Germany	30	9535	28	13	2	13
Barcelona, Spain	18	19 357	30	18	5	7
El Valles, Spain	30	5737	8	4	1	3
Styria, Austria	30	29 026	30	9	3	18
Lithuania	30	95 469	96	38	9	49
SW Ukraine	30	44 761	14	0	0	14
Tuscany, Italy	30	67 120	41	15	3	23
Leipzig, Germany	30	8745	10	3	2	5
Sicily, Italy	30	25 339	21	13	0	8
Wessex, UK	30	65 559	87	55	20	12
Oxford, UK	30	13 136	26	19	3	4
<b>Totals</b>		<b>709 030</b>	<b>761</b>	<b>375 (49.3%)</b>	<b>104 (13.6%)</b>	<b>282 (37.0%)</b>

countries with one, two or three prenatal ultrasound screenings and the lowest rate was in Lithuania, SW Ukraine and in the countries without routine screening (Table 4). Except for Lithuania and SW Ukraine, there were no differences between the

European countries with one, two or three prenatal ultrasound scans but a significant difference between countries with or without screening (17.9% vs 46.0%, and 55.6%,  $p < 0.01$  and 17.9% vs 30.5%,  $p < 0.05$ ). There was no difference between countries without

Table 3—Associated congenital heart defects: proportion of prenatal detection of cardiac malformations (CHD) and termination of pregnancy (TOP) by registries individually and according to prenatal diagnostic policies (see Table 1)

Registry	Total associated CHD	Livebirths	Fetal deaths	Prenatal diagnosis		Termination of pregnancy (TOP)		<24 Gestational weeks				
				n	%	n	%	Total screened	Prenatal diagnosis		TOP	
									n	%	n	%
Odense	13	10	0	2	15.4	3	23.0	2	2	100	12	100
Paris	78	28	1	55	70.5	49	62.8	55	41	74.5	30	54.5
N Netherlands	32	28	3	8	25.0	1	3.1	8	0	0	0	0
Strasbourg	45	14	1	36	80.0	30	66.6	36	32	88.8	26	72.2
Lausanne	40	32	2	15	37.5	6	15.0	15	9	60	5	33.3
Croatia	7	6	1	1	14.3	0	0	1	0	0	0	0
NE Italy	87	56	0	34	39.0	31	35.6	34	15	44.1	12	2.9
Basque Country	46	38	1	16	34.8	7	15.2	16	5	31.2	3	18.7
SW Netherlands	22	20	2	2	9.0	0	0	2	0	0	0	0
Mainz	28	21	3	14	50.0	4	14.3	14	4	28.5	1	7.1
Barcelona	30	8	1	16	53.3	21	70.0	16	11	68.7	9	56.2
El Valles	8	3	1	7	87.5	4	50.0	7	5	71.4	4	57.1
Styria	30	25	1	15	50.0	4	13.3	15	7	46.6	3	20
Lithuania	96	86	9	18	18.7	1	1.0	18	6	33.3	1	5.5
SW Ukraineia	14	7	1	7	50.0	6	42.8	7	3	42.8	3	42.8
Tuscany	41	32	2	25	60.0	7	17.0	25	11	44	6	24
Leipzig	10	7	1	7	70.0	2	20.0	7	4	57.1	2	28.5
Sicily	21	19	1	12	57.1	1	4.7	12	11	91.6	1	8.3
Wessex	87	51	11	37	42.5	25	28.7	37	34	91.8	20	54.4
Oxford	26	11	3	15	57.6	12	46.1	15	13	86.6	8	53.3
Totals	761	502	45	342	45.0	214	28.1	342	213	27.9	136	17.9

Table 4—Proportion of prenatal detection rate of cardiac associated malformations and termination of pregnancy according to prenatal diagnostic policies

	Total	Prenatal diagnosis		Termination of pregnancy	
		<i>n</i>	%	<i>n</i>	%
No routine US					
N Netherlands	67	12	17.9	4	5.9
SW Netherlands					
Odense					
One US examination					
Oxford	113	52	46.0	37	32.7
Wessex					
Two US examinations					
Lausanne	70	30	42.8	10	14.3
Styria					
Lithuania	110	25	22.7	7	6.3
SW Ukraine					
TOTAL	180	55	30.5	17	9.4
Three US examinations					
Sicily, Tuscany, NE	401	223	55.6	156	38.9
Italy, Mainz, Leipzig,					
El Valles, Barcelona,					
Basque Country, Paris,					
Strasbourg, Croatia					

US, Fetal ultrasonographic examination.

screening and Lithuania and SW Ukraine but there was a significant difference between countries without screening and Lausanne and Styria ( $p < 0.05$ ).

Concerning TOP there was again a significant difference between the countries with no screening and the countries with one ( $p < 0.01$ ) and three scans ( $p < 0.01$ ). There was no difference between the countries with no screening and the countries with two scans. However there was a difference between Styria and Lausanne, and between Lithuania and SW Ukraine ( $p < 0.05$ ).

Of 375 CHD cases with chromosomal anomalies, there were 239 Down syndrome, 59 trisomies 18, 34 trisomies 13 and 14 Turner syndrome; 39 cases had other chromosomal anomalies. Table 5 shows the CHD present in the cases with chromosomal anomalies. A total of 86/375 cases were terminated (22.9%), 210 were livebirths (56.0%) and the others were fetal deaths (21.0%). Of 150 livebirths with Down syndrome, 88 were from mothers under 35 years of age (58.7%), 32 from mothers aged 36 or 37 years (21.3%) and 30 from mothers over 37 years of age (20.0%). Maternal age was not known for five cases. For trisomy 13, 12/34 cases were livebirths (35.3%), and 21/59 cases with trisomy 18 were livebirths (35.6%).

Table 6 shows the 104 recognized syndromes.

There were 282 cases of CHD with other malformations that were non-chromosomal and not part of recognizable syndromes. Table 7 shows the CHD of these 282 multiply malformed cases.

The varieties of CHD present in the three types of malformations cases, recognized syndromes, chromo-

somal and multiply malformed, are shown in Table 7 with their detection rate, the percentage of termination and the mean gestational age at diagnosis.

Table 8 shows the prenatal detection rate and the percentage of termination according to the type of malformation. The detection rate was higher in non-chromosomal recognized syndromes and in multiply malformed than in chromosomal anomalies. However the difference was not significant.

Table 9 shows the prenatal detection rate of fetal congenital heart defects by ultrasonographic examination according to maternal age and to the type of malformation: chromosomal, recognized non-chromosomal syndrome and multiply malformed non-chromosomal and non-syndromic. As can be seen from Table 9, there is no difference in detection rate regarding the type of malformation before a maternal age of 35 years ( $p = 0.17$ ). However, after maternal age 35 years there is a trend towards chromosomal anomaly ( $p = 0.08$ ) as the detection rate is lower in this age group.

## DISCUSSION

Overall prenatal detection rate of CHD was performed in 45.0% of the associated cases of CHD which is close to three times more than in isolated cases ( $p < 0.01$ ) (Garne *et al.*, in press). The detection rate was higher for syndromic cases and for multiply malformed infants than for chromosomal cases (Table 9).

Regarding maternal age, there was no difference between these three categories of malformations before 35 years of age. However after 35 years of age there was a trend towards chromosomal anomaly (Table 9) which is an unexpected finding as pregnancies of mothers in this age group are usually more closely monitored than are the pregnancies of younger mothers as they are at higher risk for chromosomal anomalies.

This overall higher detection rate for associated

Table 5—Congenital heart defects (CHD) present in the cases with chromosomal anomalies

	Trisomy 21	Trisomy 18	Trisomy 13	Turner syndrome
AVSD	76	4	2	
VSD	68	38	6	
ASD	51	4	1	
Common ventricle	1	2		1
Tetralogy of Fallot	4		4	
CoA			3	7
Complex cardiopathy	3	3	5	1
Other	36	8	13	5
<b>Totals</b>	<b>239</b>	<b>59</b>	<b>34</b>	<b>14</b>

AVSD, Atrio-ventricular septal defect; VSD, ventricular septal defect; ASD, auricular septal defect; CoA, coarctation of aorta; complex, association of two or more CHD.

Other defects include hypoplastic left heart, double outlet right ventricle, pulmonary atresia, aortic atresia, aortic stenosis and unspecified CHD.

Table 6—Recognized syndromes with associated congenital heart defects (CHD)

Total	Syndrome	CHD	Prenatal diagnosis		TOP
			<i>n</i>	%	
28	Deletion 22q11	25 Conotruncal, 3 VSD	12	44.4	7
1	Aarskog syndrome	VSD	0		
1	Acardia-anencephaly		1		1
1	Amniotic bands syndrome	HLH	1		1
2	Pentalogy of Cantrel	Exstrophy of heart	2		2
1	Cerebro-costo-mandibular syndrome	VSD	1		
3	CHARGE association	2 VSD, ASD	0		
2	Chondrodysplasia punctata (rhizomelic)	2 VSD	1		
2	Ellis-van Creveld syndrome	VSD, AVSD	2		1
4	Fetal alcohol syndrome	3 VSD, 1 ASD	2		1
1	Syndrome of Franceschetti	VSD	0		
2	Fryns syndrome	2 VSD	2		1
1	Goldenhar syndrome	VSD	0		
1	Greig syndrome	ASD	1		
2	Holt-Oram syndrome	ASD, complex CHD	0		
17	Situs inversus	Dextrocardia, CAV, 2 TGA, 2 ASD, 5 complex, HLH, VSD	11	64.7	9
1	Multiple pterygium syndrome	ASD	0		
1	Neonatal Marfan syndrome	Complex	0		
4	Noonan syndrome	3 PS, 1 complex	2		
2	Oto-facio-digital syndrome	1 complex, 1 VSD	2		1
2	Pierre Robin sequence	1 ASD, 1 VSD	0		
1	Prader Willi syndrome	VSD	0		
1	Roberts syndrome	Complex	1		1
1	Robinow syndrome	VSD	0		
1	Simson-Golabi-Behmel syndrome	ASD	1		
4	Skeletal dysplasia	1 complex, 2 VSD, 1 ASD	3		2
1	Smith Lemli Opitz syndrome Type 2	1 complex	1		
15	VATER association	3 Fallot, 5 complex, tricuspid atresia, 3 ASD, 2 VSD	7	46.6	5
1	Zellweger syndrome	VSD	0		

VSD, Ventricular septal defect; HLH, hypoplasia left heart; ASD, atrial septal defect; AVSD, atrio-ventricular septal defect; TGA, transposition of great arteries; PS, pulmonary stenosis; Fallot, tetralogy of Fallot; complex, association of two or more CHD; TOP, termination of pregnancy.

CHD compared to isolated CHD (Garne *et al.*, in press) is present for all types of CHD (Table 7), i.e. atrial septal defect 8% vs 31.8% ( $p < 0.01$ ), ventricular septal defect 7% vs 40.2% ( $p < 0.01$ ), common truncus arteriosus 18% vs 64.7%, transposition of great arteries 20% vs 50.0% ( $p < 0.01$ ), tetralogy of Fallot 15% vs 50% ( $p < 0.01$ ), tricuspid atresia 40% vs 83.3%, pulmonary stenosis 11% vs 50% ( $p < 0.01$ ), aortic stenosis 3% vs 57.1%, coarctation of aorta 16% vs 52.0% ( $p < 0.01$ ), total arterio-pulmonary venous return 0% vs 57.1%, and complex cardiopathy 34% vs 75.0% ( $p < 0.01$ ). However this is not the case for severe CHD: hypoplastic left heart 60% vs 69.2% non-significant (NS), single ventricle 50% vs 68.7% (NS) and atrio-ventricular septal defect (AVSD) 56% vs 39.8% (NS). The fact that AVSD is detectable by four-chamber view and this view is recommended as part of obstetric ultrasonographic evaluation (Allan, 1999) may explain this high detection rate. Moreover, AVSD is a common CHD occurring in several conditions, especially Down syndrome (Ferencz *et al.*, 1989).

Chromosomal anomalies were the more numerous

associated CHD accounting for half of the cases, followed by multiple malformations (37%). Among the 375 chromosomal anomalies, trisomy 21 accounted for 63.7% of the cases with three main CHD: auriculo-ventricular septal defect (31.2% of the cases), ventricular septal defect (28.4%) and atrial septal defect (21.3%). Ventricular septal defect was the more frequent defect in trisomy 13 (64.4% of the cases) in addition to trisomy 18 (17.6%). Half of the 14 cases with Turner syndrome had a coarctation of aorta. These prevalences were expected (De Grouchy and Turleau, 1982). However, as was shown by Van Karnebeek and Hennekam (1999), lesions of many chromosome regions can be associated with CHD. Prenatal diagnosis was performed in 40.3% of the cases with chromosomal anomalies.

Of the syndromic cases, 28/104 had a deletion 22q11 (26.9%), 17 had a situs inversus (16.3%) and 15 were a VATER association (14.4%). Johnson *et al.* (1997) identified, over a 6.5-year period, 57 patients with chromosomal abnormalities and CHD; of these 37 had 22q11 deletions. Prenatal detection was performed in

Table 7—Associated congenital heart defects: number, prenatal detection rate (PND), termination of pregnancy (TOP) and gestational age (GW in weeks) at detection

		PND		TOP		
	<i>n</i>	<i>n</i>	%	<i>n</i>	%	GW
Atrio-ventricular septal defect						
Total	98	39	39.8	19	19.4	24 (11–39)
Chromosomal	89	32	35.9	16	17.9	21 (11–36)
Multiple	6	4	66.6	2	33.3	19–29
Syndromic	3	3	100.0	1	33.3	26–30
Pulmonary atresia						
Total	19	9	47.4	4	21.0	22 (19–35)
Chromosomal	4	3	75.0	1	25.0	19–22
Multiple	6	4	66.6	1	16.6	19–35
Syndromic	9	2	22.2	2	22.2	14–22
Pulmonary stenosis						
Total	16	8	50	4	25.0	24 (11–34)
Chromosomal	7	4	57.1	3	42.8	14–24
Multiple	8	4	50	1	12.5	11–33
Syndromic	1	0		0		
Aortic stenosis						
Total	14	8	57.1	5	35.7	21 (11–25)
Chromosomal	4	2	50.0	1	25.0	(11)
Multiple	9	5	55.5	3	33.3	12–25
Syndromic	1	1		1		22
Coarctation of aorta						
Total	25	13	52.0	6	25.0	22 (10–34)
Chromosomal	10	6	60.0	4	40.0	11–24
Multiple	12	6	50.0	1	18.3	19–34
Syndromic	3	1	33.3	1	33.3	22
Aortic atresia						
Total	6	3	50.0	3	50.0	16–22
Chromosomal	1	1		1		16
Multiple	2	1	50.0	1	50.0	21
Syndromic	3	1	33.3	1	33.3	22
Single ventricle						
Total	16	11	68.7	6	37.5	20 (9–36)
Chromosomal	5	3	60.0	2	40.0	19–20
Multiple	8	7	87.5	4	50.0	9–26
Syndromic	3	0		0		0
Complex cardiopathy						
Total	28	21	75.0	12	42.8	20 (10–36)
Chromosomal	12	8	66.6	6	50.0	14–36
Multiple	11	10	90.9	4	36.3	13–36
Syndromic	5	3	60.0	2	40.0	17–21
Common truncus arteriosus						
Total	17	11	64.7	6	35.2	20 (14–32)
Chromosomal	5	4	80.0	2	40.0	15–32
Multiple	9	3	33.6	1	11.1	14–20
Syndromic	4	4	100.0	3	75.0	17–30
Ebstein						
Total	2					
Chromosomal	1	1		1		25
Multiple	1	0		0		
Syndromic						
Total arterio-pulmonary venous return						
Total	7	4	57.1	2	28.5	9–34
Chromosomal	2	2	100.0	1	50.0	9–34
Multiple	4	2	50.0	1	25.0	20–32
Syndromic	1	0		0		0
Tricuspid atresia						
Total	6	5	83.3	2	33.3	11–32
Chromosomal	1	1		1		17
Multiple	4	3	75.0	0		11–32
Syndromic	1	1		1		20

Table 7—Continued

	<i>n</i>	PND		TOP		GW
		<i>n</i>	%	<i>n</i>	%	
Hypoplastic left heart						
Total	26	18	69.2	11	42.3	20 (10–36)
Chromosomal	6	3	50.0	2	33.3	17–24
Multiple	14	11	78.5	6	42.8	10–36
Syndromic	6	4	66.6	4	66.6	18–20, 21
Transposition of great arteries						
Total	16	8	50.0	4	25.0	20 (13–22)
Chromosomal	2	1	50.0	2	100.0	13
Multiple	13	7	53.8	2	15.3	14–32
Syndromic	1	0		0		
Tetralogy of Fallot						
Total	50	25	50.0	11	22.0	20 (14–36)
Chromosomal	22	11	50.0	9	40.9	14–36
Multiple	21	11	52.3	2	9.5	15–34
Syndromic	7	3	42.8	0		16–23
Ventricular septal defect						
Total	276	111	40.2	74	26.8	21 (9–36)
Chromosomal	129	52	40.3	55	42.6	11–36
Multiple	109	46	42.2	13	11.9	9–36
Syndromic	38	13	34.2	6	15.7	14–32
Atrial septal defect						
Total	132	42	31.8	19	14.3	24 (13–36)
Chromosomal	72	22	30.5	15	20.8	13–36
Multiple	49	18	36.7	3	6.1	30 (14–36)
Syndromic	11	2	18.1	1	9.0	20

Table 8—Prenatal detection rate (PND) and termination of pregnancy (TOP) of associated congenital heart defects according to the type of malformation

	No PND		PND		TOP		Total
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	
Chromosomal anomalies	224	59.7	151	40.3	86	22.9	375
Non-chromosomal recognized syndromes	50	48.0	54	51.9	32	30.8	104
Multiple non-chromosomal and non-syndromic	145	51.4	137	48.6	46	16.3	282
<b>Totals</b>	<b>419</b>	<b>55.0</b>	<b>342</b>	<b>45.0</b>	<b>164</b>	<b>21.5</b>	<b>761</b>

Table 9—Detection rate of fetal associated congenital heart defects according to maternal age

	Maternal age <sup>a</sup>									
	≤ 35 years					> 35 years				
	Yes		No		Total	Yes		No		Total
	<i>n</i>	%	<i>n</i>	%		<i>n</i>	%	<i>n</i>	%	
Chromosomal anomalies	97	44.7	120	55.3	217	52	35.1	96	64.9	148
Non-chromosomal recognized syndromes	46	56.8	35	43.2	81	8	53.3	7	46.7	15
Multiply malformed non-chromosomal and non-syndrome	110	49.1	114	50.9	224	23	50.0	23	50.0	46
<b>Totals</b>	<b>253</b>	<b>48.5</b>	<b>269</b>	<b>51.5</b>	<b>522</b>	<b>83</b>	<b>39.7</b>	<b>126</b>	<b>60.3</b>	<b>209</b>

<sup>a</sup>Maternal age was not known in 30 cases.

12/28 cases with a 22q11 deletion and a CHD of the present study. Therefore in addition to chromosome analysis, a FISH analysis of this region should be considered in prenatally detected cardiac defects, especially in conotruncal defects.

Prenatal diagnosis was performed in 48.6% of the syndromic cases. In a postnatal study of CHD in Malta (Grech and Gatt, 1999) 192/231 (83%) CHD were isolated, 21 (9%) were associated with chromosomal anomalies including 19 cases of Down syndrome, four cases were syndromic (2%) and 14 cases (6%) were multiply malformed. In the present study among 2454 cases with CHD 1693 (69.0%) were isolated (Garne *et al.*, in press) and among the 761 associated cases, 375 (15.3%) were chromosomal including 239 Down syndrome, 104 (4.2%) were syndromic and 282 (11.5%) were multiply malformed.

In multiply malformed fetuses with CHD a variety of heart defects were present. However 109/262 cases had a ventricular septal defect (41.6%), 45 had an atrial septal defect (18.7%) and 21 a tetralogy of Fallot (8.0%).

There were large regional variations in prenatal detection of associated CHD. The highest rate was in the countries with three ultrasonographic scans and in the two registries from the UK with one screening scan. As two out of three scans performed in the countries with three scans are done for biometric purposes, one can conclude that one ultrasonographic scan done for research of congenital anomalies between 18 and 24 weeks' gestation is able to detect around two-thirds of associated CHD (Table 3), whereas in the registries with no routine fetal scan and in Lithuania and SW Ukraine only around 6% of the associated CHD are detected prenatally ( $p < 0.01$ ).

The large region of variation in the prenatal detection rate of associated congenital heart disease has several reasons. In the UK scanning is performed by radiographers whereas in the other countries most of the scans were performed by obstetricians and midwives. The quality of the equipment was not the same for the various centres; equipment quality was low in Lithuania and SW Ukraine where the detection rate was lower than in the other centres.

Mean gestational age at prenatal detection of the associated CHD was less than or equal to 24 weeks (Table 7) which is below the upper limit for TOP in most European countries (Table 1). If taking the decision whether or not to terminate a pregnancy after prenatal detection of an isolated cardiac defect raises many questions (Garne *et al.*, in press), the decision here is less questionable as for instance half of the associated CHD are chromosomal anomalies (Table 2), and close to 50% of the syndromic cases are 22q11 deletion (Table 6). The other associated defects are usually severe congenital anomalies, syndromic or multiply malformed.

During a period of 10 and 4 years, respectively, 1984–1993, Dillon and Walton (1997) and Stoll *et al.* (1998) identified antenatally 438 cases and 779 fetuses with a congenital anomaly. Identification of cardiac lesion was poor. Only 9.8% and 10.2%, respectively of

the isolated cardiac abnormalities were identified antenatally. Diverse studies of routine scanning of fetal malformations are not strictly comparable because of population differences, methods and timing of scans. However, sensitivities of detection are low, particularly when detection below 24 weeks is considered: 5% (Lys *et al.*, 1989), 22% (Rosendahl and Kivinen, 1989), 28% (Macquart-Moulin *et al.*, 1989) and 20.1% (Stoll *et al.*, 1993). Most of these studies do not consider separately isolated and associated CHD. In the study of Stoll *et al.* (1998) the prenatal detection rate of CHD was three times higher for associated CHD (33.0%) than for isolated CHD. In the recent published studies of Grandjean *et al.* (1999) and Klein *et al.* (1999), the detection rate of major CHD was around less than 50% but for common truncus (59.1%) and coarctation of aorta (54.5%) (Grandjean *et al.*, 1999) and 51.3% for AVSD and 63.4% for absence/severe hypoplasia of a ventricle (Klein *et al.*, 1999). Previous studies have shown that the sensitivity of detection of fetal CHD is higher when the screening test is carried out in one ultrasound unit and lower when results come from multicentre studies (Todros *et al.*, 1997) as in the present investigations.

All these investigations were performed routinely for detection of fetal anomalies but not for specifically diagnosing CHD.

Numerous cardiac anomalies can be detected by prenatal ultrasound in specialist hands (Copel *et al.*, 1987; Allan, 1988; Davis *et al.*, 1990; Hess *et al.*, 1990; Chitty *et al.*, 1991). The four-chamber view is the optimum screening test for CHD as it has a very high specificity. At least 12 reports appear to have specifically screened antenatal populations using the four-chamber view (Fremont *et al.*, 1986; Hegge *et al.*, 1987; Sharland and Allan, 1992; Bromley *et al.*, 1992; Kirk and Riggs, 1994; Schultz *et al.*, 1994; Ott, 1995; Rustico *et al.*, 1995; Buskins *et al.*, 1996; Todros *et al.*, 1997; Fernandez *et al.*, 1998; Leung *et al.*, 1999). The four-chamber view alone should detect hypoplastic left heart, single ventricle, mitral/tricuspid/pulmonary atresia, double inlet ventricle, Ebstein's anomaly, atrioventricular canal, large septal defects, tetralogy of Fallot, ectopia cordis, and atrial isomerism (Constantine and McCormack, 1991).

Achiron *et al.* (1992) offered screening for CHD to all pregnant women (5347 fetuses) routinely attending an obstetric ultrasonographic unit at a medical centre in Jerusalem. This study was performed for comparison of extended fetal echocardiography with the standard four-chamber view in detecting cardiac abnormalities. The extended fetal heart examination detected 86% (18/21) of major abnormalities. In such circumstances, a large variety and a wide proportion of defects can be detected. Rustico *et al.* (1995) excluded the less severe cardiac anomalies (ventricular septal defect and auricular septal defect) in their study of 7025 women at low risk for CHD screened at 20–22 weeks' gestation. The sensitivity for major CHD was 61.3%.

In the study of Kirk and Riggs (1994) 5111 fetuses



were analysed using the four-chamber view and 24 CHD out of 51 were detected (47%).

In a specialized centre where patients at high risk for CHD are referred, 3246 fetuses were examined between 16 and 25 weeks of gestation (Buskins *et al.*, 1996). A total of 24/47 cardiac anomalies were detected (43%). However, the accuracy of the four-chamber view as a screening test for detection of CHD prenatally in a low-risk population is far from being so high in routine practice as was shown by the study of Todros *et al.* (1997). Seventeen obstetric units of the Piemonte Region (Italy) participated in the study. At each routine scan from 18 weeks of gestational age, the four chambers of the heart were looked for, and 11 232 sonograms were performed in 8299 pregnancies. The sensitivity was only 15%. When malformations that are not associated with an abnormal four-chamber view were excluded from the analysis, the sensitivity increased to 35.3%. The sensitivity found in this study, as in the present study, is low, but it is probably realistic since it is comparable with that reported in other multicentre studies (Todros *et al.*, 1997).

The sensitivity of the screening test may be improved with the analysis of the great arteries as was shown by Kirk and Riggs (1994) and Achiron *et al.* (1992). With the analysis of the great arteries the detection rate increased from 47% to 78% and from 48% to 78%, respectively.

Another means of improving the sensitivity of the screening test might be to improve staff training, as was demonstrated by Sharlan and Allan (1992) who were able to achieve a sensitivity of 69% for CHD detectable on the four-chamber view by providing formal training to the operators working in the units involved in their multicentre study.

In the present study the accuracy of routine 'first level' prenatal ultrasonographic examination was assessed. When all non-chromosomal malformations were taken into consideration the sensitivity of the screening for associated CHD was only around 50%. However the sensitivity of detection varied from 40% for malformations such as AVSD and ventricular septal defect to 69.2% for hypoplastic left heart and 75% for complex CHD. Ultrasonographic evaluation of the fetal heart has been estimated to detect two abnormalities per 1000 in a general population. According to Allan *et al.* (1986), a screening program would not detect all CHD but should detect over 60% of severe structural heart disease that present in the first year of life. If the great arteries are also examined, over 90% of major heart disease could be detectable prenatally (Allan, 2000).

The present results stress the need to perform one scan for research of CHD between 18 and 24 weeks of gestation, to train sonographers, to obtain a definite clear four-chamber view, and to incorporate into routine prenatal ultrasonographic scanning the extended fetal heart examination proposed by Achiron *et al.* (1992), Sharland and Allan (1992) and Allan (2000) in order to improve the prenatal detection of congenital heart disease, and to obtain homogeneity of

expertise among the European centres. However it should be borne in mind that the purpose of fetal echocardiography is not to terminate all affected pregnancies, but to provide information and optimum care for the patient (Allan, 1995; Sharland, 1997).

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