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The association between congenital heart disease and Down syndrome in prenatal life

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ABSTRACT

Objective *To assess the relationship between congenital heart disease (CHD) and Down syndrome (DS) in utero.*

Design *Retrospective case series.*

Subjects *Fifty-two fetuses with a cytogenetic diagnosis of DS managed at our Fetal Cardiology Unit in the study period. In particular, two populations of fetuses with DS were studied: a group of 41 DS fetuses referred to our unit for fetal echocardiography due to the chromosomal anomaly and a second group of 274 fetuses referred because of suspected CHD, 11 of which were found to have DS.*

Methods *All fetuses were submitted to detailed ultrasound evaluation of fetal anatomy. Associated extra-cardiac anomalies, and presence and type of CHD, were recorded for all fetuses. Karyotyping was obtained by means of cordocentesis or amniocentesis. Necropsy or neonatal echocardiograms were sought for confirmation of the prenatal diagnosis.*

Results *In the group of 41 fetuses with known DS, the incidence of CHD was 56% ([atrioventricular septal defect (AVSD) 44%, ventricular septal defect (VSD) 48%], the remainder having other heart defects). Conversely, considering the incidence of DS in fetuses with CHD, 43% of all AVSDs (53% of AVSD with normal visceral situs) were associated with DS, whereas none of the 39 cases of VSD was associated with trisomy 21. Ventricular septal defects were diagnosed only in fetuses referred to our center with a known diagnosis of aneuploidy.*

Conclusions *We have confined that more than half of the fetuses with DS bear a CHD, which is an AVSD in 44% of cases. Conversely, 43% of fetuses with an AVSD have trisomy 21. For VSDS, the situation is controversial, due to the relatively low detection level of this heart defect at the routine mid-trimester obstetric scan.*

INTRODUCTION

The association between Down syndrome (DS) and congenital heart disease (CHD) has been well established since 1950, when the incidence and the type of CHD present in newborns and infants with DS was thoroughly described[1]. Since then several cohort studies, such as the Baltimore–Washington Infant Study (BWIS)[2,3] and the New South Wales study[4], have significantly contributed to the definition of the close relationship between DS and CHD. The same studies have also demonstrated that the types of malformation most commonly associated with trisomy 21 are the atrio-ventricular and ventricular septal defects (AVSD and VSD), which together account for 76% of all CHD seen in neonates with DS[3]. Only a minority of infants with DS have other lesions such as tetralogy of Fallot/double outlet right ventricle (7%) or coarctation of the aorta (2%). When fetal echocardiography was introduced into clinical practice[5], it became possible to study the spectrum of lesions associated with DS in prenatal life. Since then, several authors have reported the higher incidence of chromosomal anomalies, including trisomy 21, in fetuses with CHD in comparison with postnatal data. In particular, abnormal karyotypes have been found in 16–45% of fetuses with CHD compared with 5–10% of newborns with CHD[6–8]. However, in most series, fetal karyotyping was prompted by the disclosure of the heart defect and/or associated extra-cardiac anomalies[9]. To the best of our knowledge, no study has appeared in the literature reporting a detailed study of cardiac anatomy in fetuses with a previously ascertained diagnosis of aneuploidy.

We report here on: (1) the incidence of CHD in a group of 41 fetuses in which the diagnosis of trisomy 21 had been ascertained prior to echocardiography by means of amniocentesis performed for advanced maternal age, abnormal serum screening or the presence of extra-cardiac malformations; and (2) the incidence of DS in a population of 274 cases of fetuses with CHD referred to our unit for fetal

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echocardiography. The objective of this study was to define the relationship between DS and CHD in prenatal life.

MATERIALS AND METHODS

Representativeness of the sample

Currently, health policies aimed at prenatal detection of DS approved by our local health authority include the offer of karyotyping (amniocentesis) to all women > 35 years of age, and 2nd trimester biochemical serum screening by means of combined evaluation of free β-hCG, estriol and α-fetoprotein (triple test) to the remaining population of pregnant women. In case of a screen-positive test, the woman is then offered amniocentesis. Our department is one of the only two regional referral centers to which women with such an indication for aminocentesis are referred. As far as DS is concerned, there is no preferential referral to either of the two centers.

As for prenatal detection of CHD, our unit is the only tertiary referral centre for such anomalies. In addition, a screening program for *in utero* detection of CHD was introduced in 1994. Since then, this program, aimed at the detection of CHD by evaluation of the four-chamber view and the outflow tracts, has been implemented and coordinated by our unit. Therefore, in our area, all pregnancies in which a suspicion of fetal CHD is raised at the 2nd trimester anomaly scan, or with specific indications for fetal echocardiography are referred to our hospital.

Design and length of the study

Retrospective case series. Study period: January 1994–December 1997.

Subjects

Forty-one fetuses referred to our institution because of DS and 274 fetuses referred because of specific indications for fetal echocardiography and found to have a CHD.

Ultrasound assessment and karyotyping

All fetuses underwent complete ultrasound evaluation of fetal anatomy including fetal echocardiography. In the 41 cases referred for DS, the diagnosis of aneuploidy was already known at the time of fetal echocardiography and represented the reason for referral. In the group of 274 cases referred for fetal echocardiography, karyotyping was obtained by aminocentesis or cordocentesis. Necropsy and/or postnatal echocardiograms were sought for confirmation of prenatal diagnosis and were reviewed for all fetuses/neonates.

Statistical analysis

This was performed using the SPSS 8.0 package (SPSS, IL, USA). The two-tailed *t*-test was used to evaluate intergroup differences. *P*-values of < 0.05 were considered statistically significant. Confidence intervals of 95% were calculated for primary results.

RESULTS

A total of 52 fetuses with DS were included in the study. Maternal age at diagnosis was < 35 years in 22 cases (42.3%). Mean maternal age was 29 years in the serum screening group and 33 years in the group referred because of suspected CHD, but this difference was not statistically significant. In the latter group, three women > 35 years had refused amniocentesis prior to the diagnosis of CHD (but requested it afterwards). Mean gestational age at diagnosis (of DS + CHD) was 24 weeks (SD 5.9) with a median of 22 weeks. The mean gestational age was lower (21.2 weeks) in the group of fetuses with known chromosomal anomalies compared to the group referred because of suspected malformations (24.6 weeks), although the difference was not statistically significant.

All 52 fetuses found to have DS (41 in the serum screening group and 11 in the suspected CHD group) had a regular trisomy 21, resulting from nondisjunction. Associated extracardiac malformations were present in eight cases and are reported in Table 1. None of the 19 cases of AVSDs was associated with abnormal visceral situs. Ten of

Table 1 Extra-cardiac anomalies detected in fetuses with trisomy 21

No.	*Gestational age at diagnosis (weeks)*	*CHD*	*Associated anomalies*
1	21	VSD	Dandy–Walker + clubfoot
2	21	AVSD	ACC
3	23	AVSD	SUA
4	18	AVSD + COA	Hydrocephalus + hydrops
5	22	VSD	Clubfoot + SUA
6	21	COA	Transient mild cystic hygroma
7	38	AVSD	Unilateral renal dysplasia
8	21	AVSD	Hydrops + clubfoot

ACC = agenesis of the corpus callosum; AVSD = atrio-ventricular septal defect; CHD = congenital heart defect; COA = coarctation of the aorta; SUA = single umbilical artery; VSD = ventricular septal defect.

Table 2 Incidence of aneuploidy, and of DS, among the 274 fetuses with CHD seen during the study period (only CHD associated with DS are reported−41 cases referred for known DS were excluded)

Type of CHD	*No.*	*Isolated* n (%)	*With aneuploidy* n (%)	*With trisomy 21* n (%)
AVSD	21	11ÿ*(52%)	10ÿ(48%)	9 (43%)
VSD	39	25ÿ(64%)	14ÿ(36%)†	–
Fallot	13	9ÿ(69%)	4ÿ(31%)‡	1 (8%)
DORV	21	18ÿ(86%)	3ÿ(14%)§	1 (5%)
COARCT	14	10ÿ(71%)	4ÿ(29%)¶	–

AVSD = atrio-ventricular septal defect; CHD = congenital heart defect; COARCT = coarctation of the aorta; DORV = double outlet right ventricle; DS = Down syndrome; VSD = ventricular septal defect.*Four cases were associated with atrial isomerism; †trisomy 18 was present in 13 cases and trisomy 13 in one case; ‡trisomy 18 was present in three cases; §trisomy 18 was present in two cases; ¶trisomy 18 was present in four cases.

the 11 VSDs were peri-membranous, involving the inlet portion of the septum.

There were 44 terminations of pregnancies, one intra-uterine death, and three neonatal deaths (severe fetal growth restriction), while four neonates are currently alive and awaiting surgery.

Congenital heart disease in Down syndrome

In the group of 41 fetuses in which DS was already known at the time of fetal echocardiography, indications for karyotyping, performed by means of amniocentesis at 16–17 weeks' gestation, were: advanced maternal age in 29 cases (70.7%), positive serum screening in nine cases (22%) and presence of an extra-cardiac anomaly in three cases (7.3%) [one case each of hydrops (ascites + hydrothorax), bilateral pyelectasis + nuchal fold (6 mm) and mild cystic hygroma (resolving after 2 weeks)]. Among these 41 fetuses, 23 (56.1%: confidence interval: 40–72) demonstrated a CHD. The following types of CHD were detected: 11 cases of VSD, 10 cases of AVSD, one case of tetralogy of Fallot and one case of coarctation. Extra-cardiac anomalies were present in only two cases (clubfoot in one case and unilateral hydronephrosis in the other).

Down syndrome in congenital heart disease

During the study period (1994–1997) 297 cases of CHD were detected in 2955 pregnancies with specific risk factors undergoing fetal echocardiography. Excluding from this population the 41 cases in which the diagnosis of DS represented the indication for echocardiography, we are left with 274 CHD in 2914 high-risk patients. Karyotyping was performed in 234 (85.4%) of these 274 cases. It was not performed in the remaining 40 cases for the following reasons: CHD not associated with aneuploidies (complete transposition of the great arteries or polysplenia–asplenia syndromes, 15 cases), maternal (13 cases), late 3rd trimester diagnosis (six cases), intrauterine death prior to karyotyping (four cases) and amniocytes coulture failure (two cases). Eleven fetuses were found to have DS [4.7% of the 234 karyotyped fetuses (confidence interval: 1.9–7.3)]. The type of CHD and the incidence of DS by type of CHD in this population is reported in Table 2. As is evident, 43% of all AVSDs (53% of AVSD with normal visceral situs) were associated with DS, whereas none of the 39 cases of VSD was associated with trisomy 21, despite the 36% aneuploidy rate.

Type of CHD by type of referral (suspicion of CHD vs. known aneuploidy) is shown in Table 3. As is evident, 48% (11/23) of the 41 fetuses with a previously known diagnosis of DS had a VSD, whereas none of the 11 fetuses in which the detection of CHD led to karyotyping had a VSD. There were 49 correct diagnoses (31 true positive and 18 true negative cases) of fetal echocardiography from the total population of 52 trisomic fetuses, one incorrect diagnosis (tetralogy of Fallot diagnosed prenatally as double outlet right ventricle), one false positive case (VSD) and one false negative case (VSD).

DISCUSSION

The main objective of this study was investigate the association between DS and CHD in prenatal life. In particular, we wanted to study the incidence of CHD in fetuses with DS and, conversely, the incidence of DS in fetuses with CHD. In doing so, we searched Medline in order to find other studies reporting on CHD and DS in prenatal life. We were able to retrieve a number of CHD series from which it was possible to extract data on the incidence of DS in fetuses with CHD. By contrast, we could find only a few detailed studies on the incidence of CHD in fetuses with DS, since most papers dealing with DS and malformations in the fetus did not include an extended evaluation of the heart. Hyett *et al.*[10] reported on the incidence of necropsy-ascertained CHD in 36 fetuses with trisomy 21, in which karyotyping was prompted by an

Table 3 Type of CHD by indication for karyotyping in the group of 34 fetuses with DS and CHD

Type of referral	*AVSD*	*VSD*	*Fallot*	*DORV*	*COA*
Advanced maternal age or positive serum screening	9	10ÿ	1	–	–
Extra-cardiac malformation	1	1ÿ	–	–	1
Suspicion of CHD	9	–ÿ	1	1	–

ASVD = atrio-ventricular septal defect; CHD = congenital heart defect; COARCT = coarctation of the aorta; DORV = double outlet right ventricle; DS = Down syndrome; VSD = ventricular septal defect.

increased nuchal translucency thickness. In this population, the incidence of CHD was 55.5% (20/36). Among the 20 trisomic fetuses with CHD, 60% had an AVSD and 40% had a VSD. Fifty-five per cent was also the association rate reported by Wessels *et al.*[9] in a population of 55 fetuses with DS. Among these 55 fetuses, 33% had an AVSD and 42% a VSD, the remainder having other types of CHD. In our study, the incidence of CHD in the set of 41 DS fetuses was 56% (23/41), which is consistent with both the previously mentioned studies and postnatal data. In fact, a report on major congenital malformations in DS from three national hospital or population based registries (Central-East France, Italy and Sweden[11]) yields an incidence of CHD in DS neonates ranging from 25% to 38%. If we consider that these types of registries, due to the method of data collection, usually underestimate the true rate of major malformations by roughly 30%[12,13], then we reach the usually quoted figure of 40–50%[1]. It may be argued that both the present study and the series of Hyett *et al.*[10] tend to overestimate the real incidence of CHD due to a selection bias: in fact, in the latter series fetuses had been karyotyped because of increased nuchal translucency. Increased nuchal translucency has been demonstrated to be significantly associated with CHD regardless of karyotype[14]. As to the present series, even if we exclude from the analysis the fetuses referred due to suspicion of a heart defect, the relatively high number of cases recruited on the basis of advanced maternal age (29 cases = 70.7%) may have selected an older population of women. Since it has recently been observed that DS fetuses of teenage mothers have significantly less CHD than DS fetuses of mothers of more advanced age[11], this might have biased our series. However, in the present study, maternal age was < 35 years in 22 cases, representing 42.3% of the population.

Taking into consideration the single types of CHD, our figure regarding the incidence of AVSD in DS fetuses (44%) is lower than that reported in fetuses by Hyett (60%)[10], and in infants by Ferencz (60%)[2], but higher than the 33% incidence of the Dutch study[9]. As for VSDS, there is a huge discrepancy between postnatal and prenatal figures: in the Baltimore–Washington Infant Study (BWIS[2]), 34 (16%) of 218 liveborns with DS and CHD had a VSD, whereas the corresponding figures in fetal series are 40%, 42% and 48% (as found by the Dutch study[9], Hyett *et al.*[10], and this report, respectively). The only possible explanation for this discrepancy is the spontaneous closure of some VSDs during intrauterine life, which has been documented in few instances[10,15].

If we now consider the association between DS and CHD from another point of view, i.e. evaluating the incidence of DS in fetuses with various types of CHD, we can confirm the strong and preferential relationship of AVSD with DS observed in postnatal life, even though fetal series[16,17] seem to yield relatively lower association rates than the 60% figure of the BWIS[2] (Table 4). Consistent with pediatric series is also a minor but constant association rate with conotruncal anomalies (7% for tetralogy of Fallot; Table 4).

The situation is completely different for VSDs, due to their extremely low intrauterine detection rate[18]. To explain the absence of trisomy 21 among the abnormal karyotypes associated with VSDs *in utero* (Table 3), we have to consider two factors: the anatomy of the defect and the relatively low incidence of DS in individuals with VSDs. Since most fetuses with VSDs do not have other extra-cardiac or chromosomal anomalies, they undergo the usual level I midtrimester scan for detection of congenital anomalies, in the course of which the integrity of the interventricular septum is verified by an operator who has not been trained in fetal echocardiography and therefore is more prone to miss a VSD which causes only a minor distortion of the four-chamber view, if any at all. Therefore, most VSDs escape prenatal diagnosis and are detected only after birth[18]. In addition, the type of VSD most commonly associated with DS is the inlet peri-membranous septal defect[19]. Its site, towards the base of the heart and below the atrio-ventricular plane (Figure 1), means that this type of VSD is easily hidden by the opening of the septal leaflets of the atrio-ventricular valves during diastole and therefore it becomes even more difficult to detect during routine obstetric ultrasound.

Another point of note is the 50% mortality rate (one infant, two early neonatal and one intrauterine death) observed in the eight continuing pregnancies. Heart defects were present in all cases. The extremely small number of cases does not allow us to draw any definite conclusion about the unusually high perinatal mortality. However, this finding is consistent with the observation that DS infants with CHD have a significantly lower life expectancy than

Table 4 Incidence of DS in fetuses and neonates with CHD

Author	*Reference*	*No. of cases*	*No. of DS (%)*	*AVSD %*	*AVSD %**	*VSD %*	*Fallot %*
Brown *et al.*	17	125	9(7)	32	35	0	7
Allan *et al.*	6–16	1006	61(6)	35	61	–	–
Present series†	–	274†	11(4)	43	53	0	8
Ferencz *et al.*‡	2	4390	385(9)	60	65	7	7

*Excluding Situs Ab. †Excluding 23 cases with a diagnosis of DS known prior to fetal echocardiography. ‡Data regarding the neonatal cohort of the Baltimore-Washington Infant Study.

ASVD = atrio-ventricular septal defect; DS = Down syndrome; VSD = ventricular septal defect; Situs Ab = visceral situs abnormalities

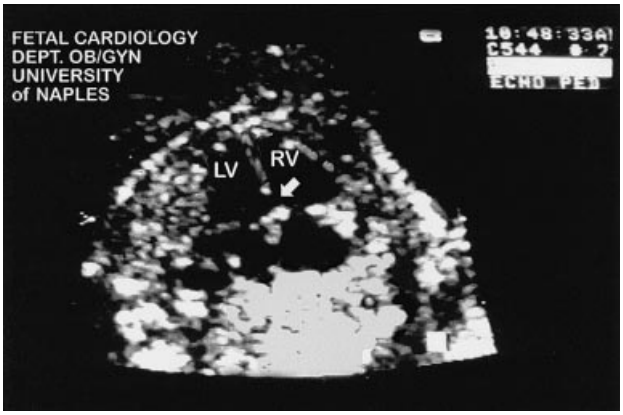

Figure 1 The type of ventricular septal defect usually associated with Down syndrome is shown: the site of the defect, the inlet perimembranous septum below the atrio-ventricular valves, is indicated by an arrow. LV = left ventricle; RV = right ventricle.

DS infants without heart defects, regardless of the type of CHD (58% vs. 78% 5-year survival rate[13]).

In conclusion, we have observed that more than half the fetuses with DS have a CHD and that 44% of these have an AVSD. Conversely, we have observed that 43% of fetuses with an AVSD have trisomy 21. As for the association rate with VSDs, the situation is heavily biased by the fact that the detection rate of this heart defect, extremely low in the general population, is even lower in DS fetuses because of the site of the defect usually associated with trisomy 21.

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