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Characterization and natural history of ventricular septal defects in the fetus

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ABSTRACT

Objective *To characterize and describe the evolution of ventricular septal defects (VSD) from intra-uterine diagnosis to infancy in a population of fetuses with isolated defects.*

Methods *Sixty-eight fetuses with isolated VSD represented the study population. Of these, 28 underwent termination of pregnancy, 14 died in utero or after birth and 26 reached 1 year of age. In this population, the following variables were evaluated: presence of extracardiac or chromosomal anomalies, site and size of the defect, pregnancy outcome. These variables were assessed against closure of the VSD up to 1 year of age. Necropsies were available for all fetuses following termination of pregnancy. All surviving neonates were followed up directly or by telephone until documented echocardiographic closure of the defect or until 1 year of age.*

Results *There was a significant correlation between type of VSD and type of aneuploidy ($P < 0.001$). A total of 26 surviving fetuses reached 1 year of age: 46.1% ($n = 12$) of all defects closed in utero, 23.1% ($n = 6$) closed during the first year of life and 30.8% ($n = 8$) remained patent. Only three (15.8%) of the 19 VSDs < 3 mm remained patent in comparison with five (71.4%) of the seven defects > 3 mm ($P < 0.05$). None of the malalignment VSDs closed, in comparison to 69% of the peri-membranous and 60% of the muscular defects.*

Conclusion *Ventricular septal defect can undergo spontaneous closure during intra-uterine life and this process depends upon the site and the size of the defect. These data may provide useful additional information to aid prenatal counseling.*

INTRODUCTION

Ventricular septal defect (VSD) represents the most common type of congenital heart disease (CHD) and accounts for 32% of all heart defects diagnosed during the first year of life[1,2]. Several authors have demonstrated that VSDs represent evolutionary lesions that can undergo spontaneous closure up to 5 years of age[3], especially when the membranous part of the septum is not involved[4]. However, there are very few data available on the natural intra-uterine course of these defects, and the possibility that VSDs can also undergo spontaneous closure during prenatal life has, to date, only been demonstrated in an autopsy report[5]. The objective of this study was to describe the characteristics and the natural history of VSD, from intra-uterine diagnosis to infancy in a population of 68 fetuses referred to our unit for diagnosis and management.

METHODS

Between January 1994 and June 1998, 365 cases of CHD were detected in 3452 pregnancies referred to our Fetal Cardiology Unit for fetal echocardiography. These cases represented a selected population demonstrating known maternal and/or fetal risk factors for CHD. All fetuses with a VSD as a component of other CHD (tetralogy of Fallot, tricuspid atresia, etc.) or associated with other CHD (VSD + coarctation) were excluded from the study. Seventy-four (20.2%) of the 365 fetuses with CHD had an isolated VSD. Of these cases six (8.1%) were excluded from the study because the necropsy reports and/or postnatal files were not available for confirmation of the prenatal diagnosis. Thus 68 cases were available for analysis. The following data were retrieved for all cases from our computerized database: indication for fetal echocardiography, gestational age at diagnosis, presence of extracardiac or chromosomal anomalies, site of the defect, size of the defect, Doppler demonstration of flow across the defect, pregnancy outcome, neonatal follow up. The site of the defect was categorized as muscular or perimembranous (Figure 1). Muscular defects included midmuscular and apical VSDs. Perimembranous defects were

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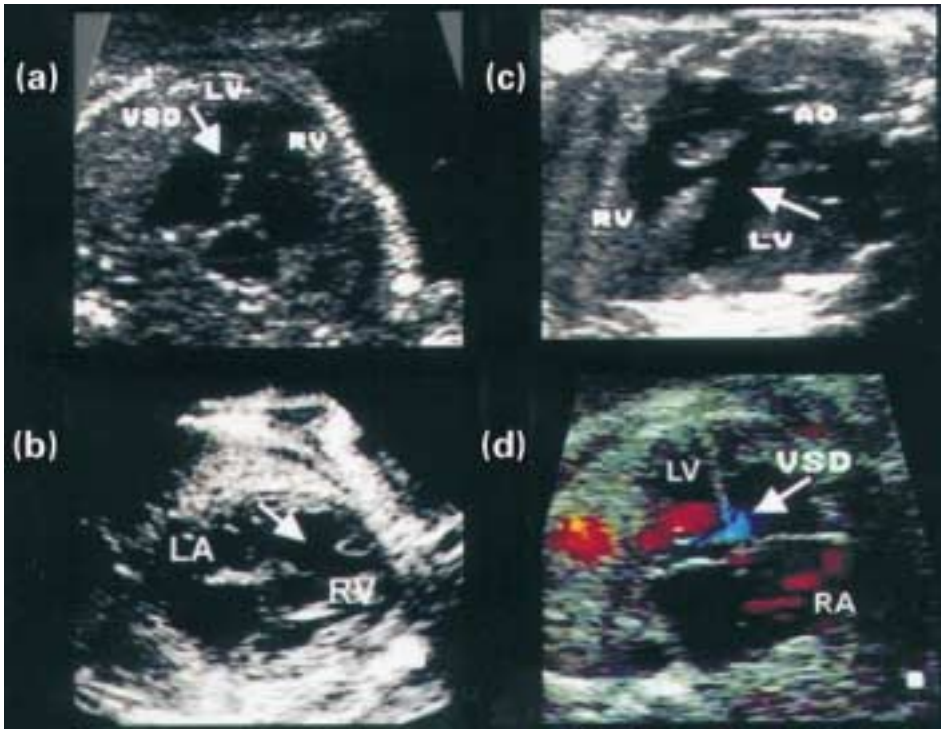

Figure 1 (a) A small (2.5 mm) mid-muscular septal defect is evident on the four chamber view (arrow). This defect closed spontaneously after 6 months of life; (b) A larger (6 mm) muscular defect, requiring surgery, is shown (arrow); (c) Long axis of the left ventricle. The malalignment defect and the overriding aorta are evident (arrow). This type of VSD is significantly associated with trisomy 18; (d) Four chamber view. A small inlet perimembranous defect and the flow across it are evident. This is the type of defect commonly associated with trisomy 21. AO, ascending aorta; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; VSD, ventricular septal defects. Arrows indicate the defects.

subdivided into inlet and outlet subtypes. Malalignment defects included both muscular and peri-membranous VSDs of the malalignment type. The size of each VSD was obtained by review of the associated videotapes. The dimensions of the defect during diastole at diagnosis and during follow up were calculated, on an off-line computer. Fetal karyotype was available in 62 of the 68 cases. Eighteen of the 26 neonates that survived the first week of life and all fetuses that died after birth due to associated chromosomal or extracardiac anomalies were examined by our pediatric cardiologist. The remaining eight neonates were followed up at other institutions. All neonates were followed up directly or by telephone until documented echocardiographic closure of the defect or until 1 year of age. Necropsies of all fetuses undergoing termination of pregnancy were performed by our perinatal pathologist.

Statistical analysis was performed with the SPSS package 8.0 for Windows '95 (SPSS, Chicago, IL, USA). The chi-squared test was used to evaluate inter-group differences.

RESULTS

The mean gestational age at diagnosis was 24.8 weeks (range 17–39 weeks). The indication for fetal echocardiography was: presence of an extracardiac malformation in 21 cases (30.9%), suspicion of CHD in 20 cases (29.4%), known aneuploidy in 17 cases (25%), fetal growth restriction in five cases (7.4%) and other indications in the remaining five cases (7.4%). Twenty-two (32.4%) of the fetuses had a perimembranous posterior inlet defect, 19 (27.9%) demonstrated a perimembranous outlet defect, 16 (23.5%) a malalignment VSD and seven (10.3%) a muscular defect. In the remaining four fetuses (5.9%), the defect could not be classified due to its dimensions (> 5 mm). The size of the defect was ≤ 2.0 mm in 21 cases (30.9%), 2.1–3.0 mm in 19 cases (27.9%), and > 3.0 mm in 28 cases (41.2%). Flow across the defect was detected by color Doppler in 51 cases (75%) overall (Figures 1D and 2A). Flow was demonstrated in 100% of VSDs > 3.0 mm and in 57.5% of smaller defects (23/40). Karyotyping was performed in 62 cases of which 29 (46.8%) were aneuploid. Thirteen cases (21%) of trisomy 18, 12 cases (19.4%) of trisomy 21, two cases of trisomy 13 (3.2%) and two cases of unbalanced translocations (3.2%) were present. The indication for echocardiography was aneuploidy in 17 cases. Excluding these 17 cases gives an adjusted aneuploidy rate of 26.6% (12/45). There was a significant correlation between the site of the defect and fetal karyotype ($P < 0.001$, Table 1). Eleven of the 12 (81.7%) fetuses with trisomy 21 and a VSD had a peri-membranous posterior defect of the inlet. This was > 5 mm in two cases. A total of 50% (two of four) of inlet defects was associated with Down syndrome. Trisomy 18 showed a preferential association with the malalignment VSD, with 69.2% (nine of 13) of the fetuses with Edwards syndrome demonstrating this type of VSD. A total of 56.3% (nine of 16) of fetuses with a malalignment VSD had trisomy 18 (Table 1). Thirty-two of the 68 fetuses

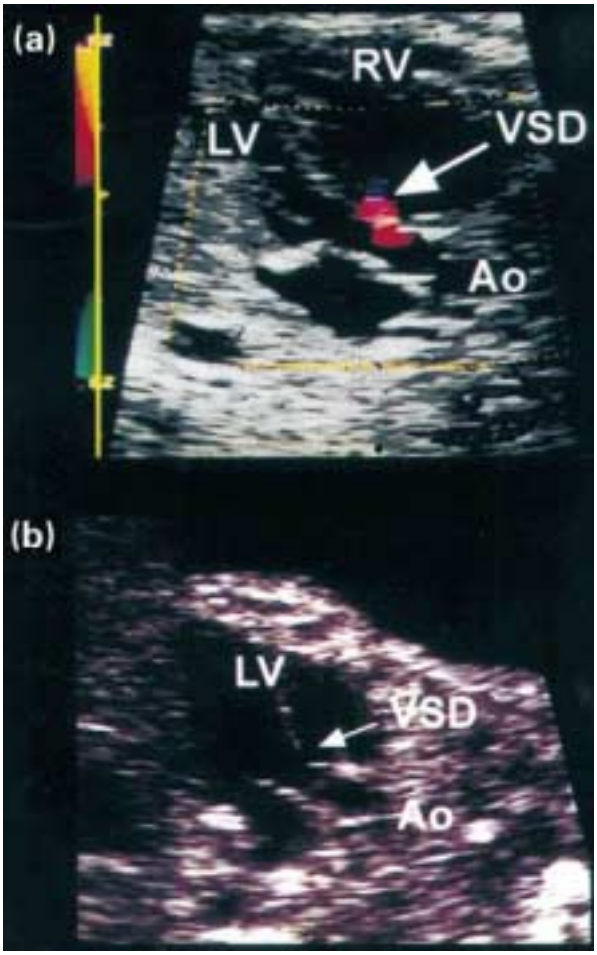

Figure 2 Long axis of the left ventricle. (a) This small defect (arrow) showed bi-directional shunting with color Doppler; (b) A similar small defect in which no flow could be detected with color Doppler and which underwent apparent intra-uterine closure. This represents a possible artifactual defect, as it was impossible to confirm its presence pre or postnatally. Ao, ascending aorta; LV, left ventricle; RV, right ventricle; VSD, ventricular septal defect.

(47.1%) had one or more extracardiac associated anomalies. There was a high association with aneuploidies in this group but 33.3% of fetuses with a normal karyotype also presented with associated extracardiac anomalies. There were 28 terminations of pregnancy (41.2%), two intra-uterine fetal deaths (2.9%), and 12 neonatal deaths (17.6%). The remaining 26 cases are alive and thriving. All fetuses undergoing termination of pregnancy had an abnormal karyotype or severe extracardiac anomalies. No termination of pregnancy was carried out in fetuses with an isolated VSD and normal karyotype.

Table 1 Fetal karyotype and site of the defect in 62 cases of prenatally detected ventricular septal defect (VSD)

	*Fetal karyotype**			
Type of VSD	*Normal n (%)*	*Trisomy 21 n (%)*	*Trisomy 18 n (%)*	*Other n (%)*
Muscular	5 (71.4)	–	1 (14.3)	1 (14.3)
Perimembranous				
inlet	8 (44.4)	9 (50)	1 (5.6)	–
outlet	15 (88.2)	1 (5.9)	1 (5.9)	–
Malalignment	4 (25.0)	–	9 (56.3)	3 (18.8)
Large VSD	1 (25.0)	2 (50)	1 (25.0)	–

* In six cases karyotype was not performed.

In order to consider the evolution of the VSD during intra-uterine and postnatal life, the 28 cases that resulted in termination of pregnancy were excluded. In the remaining population of 40 continuing pregnancies, 13 (32.5%) defects closed spontaneously *in utero* (10 before 30 weeks of gestation and three between 30 weeks and delivery), six (15%) closed during the first year of life and 21 (52.5%) remained patent. The closure rates by size and site of the defect are reported in Tables 2 and 3. Only 22.7% of the VSDs ≤ 3 mm remained patent in comparison to 88.9% of the defects >3 mm ($P < 0.001$). None of the eight malalignment VSDs closed during intra-uterine or post-natal life (Table 3). Similarly, if we consider only the 26 cases which survived the early neonatal period and reached 12 months of age, 15.8% of VSDs ≤ 3 mm remained patent in comparison to 71.4% of defects >3 mm ($P < 0.05$). All large (> 5 mm) defects and six of the eight malalignment defects were in the group of fetuses that died in the perinatal period. The overall closure rate was higher in the group of 26 fetuses which reached 12 months of age if the cases of perinatal death were included (69.2 versus 47.5%, respectively). No difference in the detection of flow across the VSD was found between cases undergoing intra-uterine closure and the remainder (five of 12 versus nine of 14). In the latter group, two of the five cases in which no trans-VSD flow could be detected *in utero* underwent spontaneous closure during the first months of life.

Only one false positive diagnosis of VSD was recorded among the other 38 cases of trisomy 21 and trisomy 18 that underwent termination of pregnancy during the study period.

DISCUSSION

This report represents an observational study on the natural history of VSD diagnosed *in utero*. The present investigation has two main limitations: first, in our institution the detection of an aneuploidy *per se* represents an indication for fetal echocardiography. This artificially increases the incidence of aneuploidies in fetuses with VSDs. Second, the intra-uterine detection rate for VSD, which is extremely low due to the fact that it represents only a minor anomaly of the four chamber view[6], differs for the various types of VSD. Unlike muscular defects, small posterior defects of the inlet and peri-membranous subaortic defects are not readily visible on the classical four chamber view but require a modified four-chamber view and a long-axis view of the left ventricle, respectively, for diagnosis. Despite these limitations, we think these data are worth reporting because of the paucity of information relating to isolated VSDs in the fetus.

As anticipated, the distribution of the various types of VSDs in our study differs from post-natal series, due to the

Table 2 Closure of ventricular septal defect (VSD) by size of the defect: (A) including all continuing pregnancies (40 cases); (B) including only neonates which reached 1 year of age (26 cases)

Size of the VSD	*Closure in utero n (%)*	*Closure after birth n (%)*	*No closure n (%)*
(A)*			
< 3 mm	11 (50.0)	6 (22.3)	5 (22.7)
3–5 mm	2 (11.1)	–	16 (88.9)
Total	13 (32.5)	6 (15.0)	21 (52.5)
(B)**			
< 3 mm	10 (52.6)	6 (31.6)	3 (15.8)
3–5 mm	2 (28.6)	–	5 (71.4)
Total	12 (46.1)	6 (23.1)	8 (30.8)

* $P < 0.001$; ** $P < 0.05$.

selection bias discussed previously. The difference is particularly marked for the muscular defects. In pediatric series these account for up to 20% of cases[7], but represented only 10.3% of cases in this fetal population. There are two possible explanations for this discrepancy. First, the relatively high number of defects such as the posterior inlet or the malalignment VSD in this series. These are usually associated with aneuploidies. Second, the detection of muscular defects is facilitated by the pressure gradient existing between the left and the right ventricles in the neonate. This determines a high velocity shunt that is easily detected by color Doppler echocardiography. Due to the physiologic patency of the ductus arteriosus and the foramen ovale this pressure gradient is absent *in utero*, rendering the diagnosis of small muscular VSDs extremely difficult in the fetus. Successful prenatal diagnosis relies mainly on the direct two-dimensional demonstration of the defect, although in some instances flow across small muscular VSDs can be demonstrated by color or pulsed-wave Doppler. However, a change in the spectrum of VSDs demonstrated in the pre- and post-natal populations, due to the selective closure of a specific type of defect, cannot be excluded.

Table 3 Closure of ventricular septal defect (VSD) by site of the defect: (A) including all continuing pregnancies (40 cases); (B) including only neonates who reached 1 year of age (26 cases)

Site of the VSD	*Closure in utero n (%)*	*Closure after birth n (%)*	*No closure n (%)*
(A)*			
Muscular	1 (16.7)	2 (33.3)	3 (50.0)
Perimembranous			
Inlet	5 (71.4)	–	2 (28.6)
Outlet	7 (43.8)	4 (25.0)	5 (31.3)
Malalignment	–	–	8 (100)
Large VSD	–	–	3 (100)
Total	13 (32.5)	6 (15.0)	21 (52.5)
(B)			
Muscular	1 (10.0)	2 (40.0)	2 (40.0)
Perimembranous			
Inlet	4 (66.7)	–	2 (33.3)
Outlet	7 (53.8)	4 (30.8)	2 (15.4)
Malalignment	–	–	2 (100)
Total	12 (46.1)	6 (23.1)	8 (30.8)

* $P < 0.001$.

We think it unlikely that the 26.6% association between VSDs and abnormal karyotype is accurate. This is because VSDs are diagnosed in the fetus principally because of associated anomalies, which in turn are associated with aneuploidies. Thus the majority of VSDs that occur as isolated lesions escape diagnosis[8–10]. This fact is also confirmed by the 33% rate of extracardiac malformations observed in fetuses with normal karyotype. Such an extremely high rate of congenital anomalies, in the absence of chromosomal aberrations, can only be explained by the fact that it was the extracardiac anomaly in these fetuses which prompted referral to level II ultrasound centers where the higher diagnostic accuracy (fetal echocardiography versus routine four chamber view screening and highly experienced versus low or moderately experienced operators) led to the subsequent identification of the VSD. However, we have confirmed the preferential association of inlet defects with Down syndrome (50%, Figure 1D) and of malalignment defects with trisomy 18 (56.3%, Figure 1C) (Table 1).

Although there are a few recent case-reports demonstrating that VSDs retain the potential to undergo spontaneous closure during prenatal life[5], we were unable to find any paper in the international literature dealing extensively with this topic. We have shown that: (I) VSDs can close *in utero* and that this event is not rare. The overall intra-uterine closure rate in this study was 32.5%; (2) the closure rate is higher for smaller defects (50% versus 11.1%, Table 2) and larger defects do not close (Table 2); and (3) the site of the defect plays a significant role in its natural history (Table 3). In particular, in cases of a malalignment VSD the defect will never close, irrespective of its size (Table 3). This is due to the type of architectural derangement inherent in its development, namely deviation of the infundibular septum (Figure 1C).

Another interesting issue concerning the site of the defect is the relatively high intra-uterine closure rate (43.8%) of small perimembranous outlet defects (Table 3, Figure 2). It is worth underlining that, in this series, all defects of this type that closed *in utero* demonstrated similar characteristics, i.e. 1.5–2.0 mm in size, subaortic location and closure by 30 weeks of gestation (Figure 2). Since such a high closure rate is unusual for outlet perimembranous defects in postnatal life[4], it might be argued that the apparent intra-uterine closure of this type of VSD may simply be the result of a false-positive diagnosis at a previous scan, due to an artefact. This impression is supported by the difficulty, in most instances, of demonstrating any flow across the defect by color Doppler. This may be due to the interference produced by the systolic ejection across the aortic orifice and/or to the small dimensions of the defect (Figure 2). However, most outlet defects (56.2%) did not close *in utero* and their presence was confirmed at autopsy or neonatal echocardiography. In addition, no difference in the detection of VSD flow was

demonstrated between cases undergoing intra-uterine closure and the others, making the hypothesis of an artifactual origin of these defects unlikely.

Finally we must consider the fact that there was only one false-positive diagnosis among the remaining 38 cases of trisomy 21 and trisomy 18 which underwent termination of pregnancy during the study period and in which no defect was found at autopsy. We believe that the relatively high spontaneous intra-uterine closure rate of VSDs in general, and of small outlet defects in particular, is real and not artifactual. It is the size of this phenomenon that needs to be confirmed with larger series. We were unable to exclude with certainty the artifactual origin in the seven cases in this study which did not show flow across the defect but underwent intra-uterine closure of the defect (Figure 2B), as neither prenatal nor neonatal confirmation of the diagnosis could be obtained.

In an elegant study of 69 autopsy specimens of hearts with perimembranous VSDs, Anderson *et al.*[11] demonstrated that almost half of the inlet defects closed anatomically or functionally whereas none of the 20 outlet VSDs showed any evidence of closure or reduction. In the inlet type of defect, the mechanism of closure involves apposition of tissue from the tricuspid leaflets or tags. However, no tissue apposition was found in outlet VSDs, probably because of their position over the central fibrous body. In our series, postnatal echocardiography showed no tag tissue at the site of the former defect. Therefore, in the fetus the closure of this type of defect must operate through a different mechanism and we hypothesize that this might involve direct sealing of the defect. This process would be favored by the absence of any pressure gradient between the two ventricular chambers (which determines a functional closure of the defect) and by the growth of the heart. Using these criteria we speculate that the late intra-uterine closure of this type of defect might represent merely a delay in the physiological development of the heart. Moreover, it is only the failure or arrest of this process at an earlier stage which is responsible for the larger defects that are referred to the pediatric cardiologist and are described in pediatric series.

These data may provide useful information during prenatal counseling for the following reasons. Fetuses in which a posterior defect of the inlet (Figure 1D) is found at mid-gestation have a 50% chance of having trisomy 21 and therefore the mother should be counseled accordingly and rapid karyotyping offered. On the contrary, parents of fetuses in which a small perimembranous subaortic defect (Figure 2) is detected should be reassured by the fact that these VSDs tend to close spontaneously in most instances. As for the possible role of an abnormal karyotype on the VSD closure rate, this could not be ascertained, due to the relatively low number of Down syndrome fetuses among the ongoing pregnancies and the fact that malalignment defects did not close, regardless of the karyotype.

The number of cases presented here, although acceptable for general analyses, needs to be expanded through larger studies to allow verification of the significance of the data from the smaller subclass categories. Despite small numbers, our study has shown that the risk of aneuploidy is strictly dependent upon the site of the defect in fetuses with isolated VSDs. In addition, we have demonstrated that VSDs can undergo spontaneous closure during intra-uterine life, and that this process is significantly correlated with the site and the size of the defect.

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