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Isolated ventricular septal defects detected by color Doppler imaging: evolution during fetal and first year of postnatal life

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KEYWORDS: color Doppler; fetal echocardiography; outcome; spontaneous closure; ventricular septal defects

ABSTRACT

Objective *To evaluate the development during gestation and up to 1 year postnatally of isolated small ventricular septal defects (VSDs) not visible by gray-scale imaging and detected only on color Doppler fetal echocardiography.*

Methods *This was a retrospective analysis of 146 fetuses with isolated VSDs detectable only on color Doppler echocardiography. Complete sequential gray-scale, color Doppler and spectral Doppler examination of the fetal heart were performed. The following variables were documented: site of the VSD, presence of extracardiac or chromosomal anomalies, outcome of the pregnancy and evolution of the defect up to 1 year postnatally.*

Results *A total of 113 fetuses reached their first year of postnatal life, 23 pregnancies were terminated, there were three stillbirths/neonatal deaths, and seven were lost to follow-up. It was observed that 32.7% (n = 37) of all defects in neonates alive after 1 year closed* in utero, *44.3% (n = 50) of defects closed spontaneously within the first postnatal year, and 23.0% (n = 26) of defects did not close. In all, a comparable number of perimembranous and muscular septal defects closed spontaneously* in utero *and during the first year of postnatal life. Among 35 fetuses with extracardiac anomalies 51.4% (n = 18) were euploid.*

Conclusion *Small VSDs, detectable only by color Doppler echocardiography, show a high spontaneous intrauterine and postnatal closure rate. These findings might be of value for prenatal parental counseling.*

INTRODUCTION

Ventricular septal defects (VSDs) represent the most common type of congenital heart defect (CHD) and account for 32% of all heart defects diagnosed during the first year of postnatal life[1,2]. The rate of spontaneous postnatal closure of VSDs varies between 11–71%[3–9]. We reviewed 146 cases referred to our prenatal ultrasound unit with isolated, small VSDs, which were detectable only by color Doppler echocardiography, and describe the characteristics and the evolution of these VSDs during pregnancy and in the first year of postnatal life.

In-utero blood pressure in both ventricles is similar, so VSDs cause no significant hemodynamic effects and the shunting of blood between both ventricles is not a problem[3–6]. If the VSD persists after birth it may allow for a left-to-right shunt. This can result in congestive heart failure or pulmonary hypertension[8]. The ventricular septum can be divided into four sections: the inlet, membranous, trabecular, and outlet components, which have different embryological origins. VSDs can exist in any of the septal locations, but can also occur at the sites of fusion between them. VSD refers to a congenital malformation in the development of the interventricular septum. The size of VSDs can vary from very small to large, sometimes involving over a third of the ventricular septum[10]. Defects might be isolated or multiple, and they are often associated with other cardiac malformations.

Prenatal sonographic diagnosis of VSDs can be difficult. One achieves the best visualization of the interventricular septum using a subcostal approach to the four-chamber view. To confirm the presence of an intact septum it should also be visualized by means of a long-axis view of the left and right ventricles together with an apex-to-base sweep along the short axis of the heart[11]. Because of artifactual areas of hypoechogenicity in the apical four-chamber

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view, a true VSD is confirmed only when it is visible in at least two different planes. Since the septum does not lie in a single plane, it can be difficult to assess the size of VSD. Color Doppler echocardiography may demonstrate bidirectional flow across the area of defect and also allow the diagnosis of a small VSD not visible on gray-scale echocardiography[12,13]. It is necessary to define which segment of the septum is involved. Careful sonographic exclusion of additional complex cardiac malformations such as tetralogy of Fallot, transposition of the great vessels, double-outlet right ventricle or other extracardiac malformations should be performed[12,14].

It has been demonstrated that VSDs can undergo spontaneous closure up to 5 years postnatally, especially when the membranous part of the septum is not involved[7,15]. VSDs can also undergo spontaneous closure during prenatal life[9]. On the other hand, when a VSD is diagnosed a likelihood of chromosomal defects must be taken into consideration[1,2]. Thus, invasive testing for fetal karyotype analysis should be offered following the prenatal diagnosis of VSD[1,2]. The aim of this study was to evaluate the development of isolated, small VSDs, not visible on gray-scale echocardiography and only detectable by color Doppler imaging, in fetuses and during early postnatal life, in a retrospective analysis of the database of a single prenatal ultrasound unit.

METHODS

This retrospective analysis included all cases ($n = 146$, 0.48%) of isolated, small VSDs, which were detected only by color Doppler flow mapping, from a total of 30 650 pregnancies referred to our prenatal diagnosis unit (referral center) of the University Hospital Lübeck, Schleswig-Holstein, Germany, between 1996 and 2004. Indications for referral to a second trimester anomaly scan and fetal echocardiography were intrauterine growth restriction, suspicion of CHD and extracardiac abnormalities. These cases represented a selected population. Ultrasound scans were performed with an ATL HDI5000 (Advanced Technology Laboratories, Bothwell, WA, USA) and an Acuson 128 XP/10 (Acuson, Mountain View, CA, USA) ultrasound machine using a 3.5-MHz or 5-MHz transducer. The high-pass filter was set at 100 Hz. Gray-scale echocardiography included visualization of the left and right ventricular outflow tract and great arteries in the four-chamber view, followed by the visualization of the three-vessel view and the basal short-axis view. Gray-scale imaging was followed by color Doppler flow mapping. Care was taken to ensure that the septum was perpendicular to the ultrasound beam, so that flow crossing the septum indicating a septal defect could be detected more accurately. Since the pressure is similar in the fetal right and left ventricles, the potential pressure gradient across a VSD is small. We therefore reduced color flow velocity to a low Nyquist limit in order to depict low-velocity jets. We confirmed any shunting across the septum by pulsed-wave Doppler interrogation of the interventricular jet. All cases with a VSD as a part of another CHD (atrioventricular septal defect, tetralogy of Fallot, tricuspid atresia, etc.) were excluded from this study.

Echocardiography was performed in all 121 liveborn neonates by our pediatric cardiologists. One neonate died 16 days after delivery due to extreme prematurity and aneuploidy (trisomy 18). Seven cases were excluded from the study because necropsy reports and/or postpartum files were not available for confirmation of the prenatal diagnosis. In all, 113 cases with isolated VSD and a complete follow-up until the first year of postnatal life were available for analysis (Figure 1). Only small muscular septal defects not detectable on gray-scale echocardiography and those which were detected by flow across the septal wall during color Doppler mapping were included. The site of defect was categorized as either muscular or perimembranous. Muscular defects included trabecular (mid-muscular and apical) VSDs and defects of the inlet and outlet septum (Figures 2–6)[16]. In one case a VSD was classified as malalignment defect and this defect was classified as an outlet defect of the septum. Fetal karyotyping following amniocentesis or fetal blood sampling by cordocentesis was performed in 76 (52%) of 146 cases.

The following data were retrieved for all cases from our computerized database: gestational age at diagnosis, presence of extracardiac or chromosomal anomalies, site

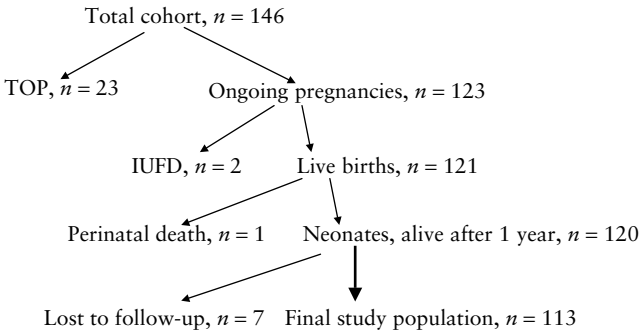

Figure 1 Flow chart of the study population. IUFD, intrauterine fetal death; TOP, termination of pregnancy.

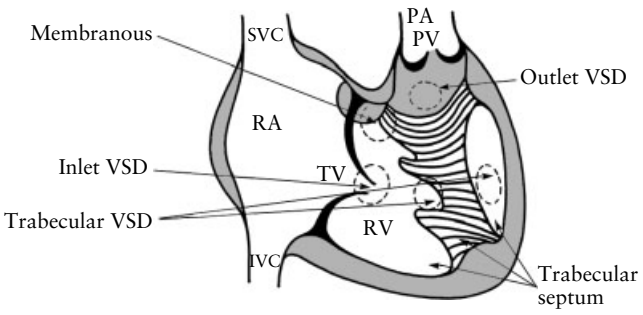

Figure 2 Diagram showing the different components of the interventricular septum and the different septal locations of ventricular septal defects viewed from the right ventricle, modified from Wenink ACG *et al.*[16]. IVC, inferior vena cava; PA, pulmonary artery; PV, pulmonary vein; RA, right atrium; RV, right ventricle; SVC, superior vena cava; TV, tricuspid valve; VSD, ventricular septal defect.

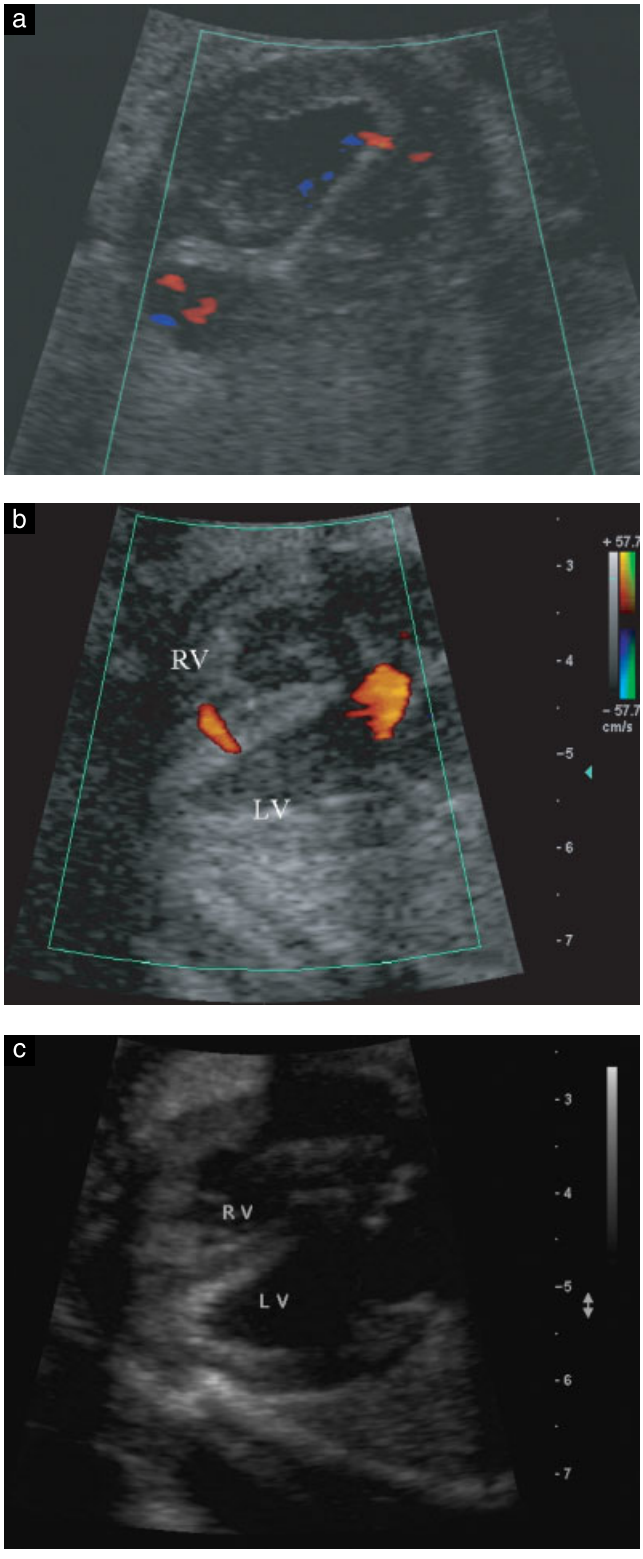

Figure 3 Color Doppler ultrasound images showing (a) small apical muscular defect, which closed during gestation, and (b) small mid-muscular trabecular defect, which closed during the first year of postnatal life. (c) Gray-scale image of the four-chamber view corresponding to that in (b). The small ventricular septal defect is not visible in this mode. LV, left ventricle; RV, right ventricle.

of the defect, Doppler demonstration of flow across the defect, necropsy report or pregnancy outcome, and neonatal follow-up. Neonates were followed up directly or

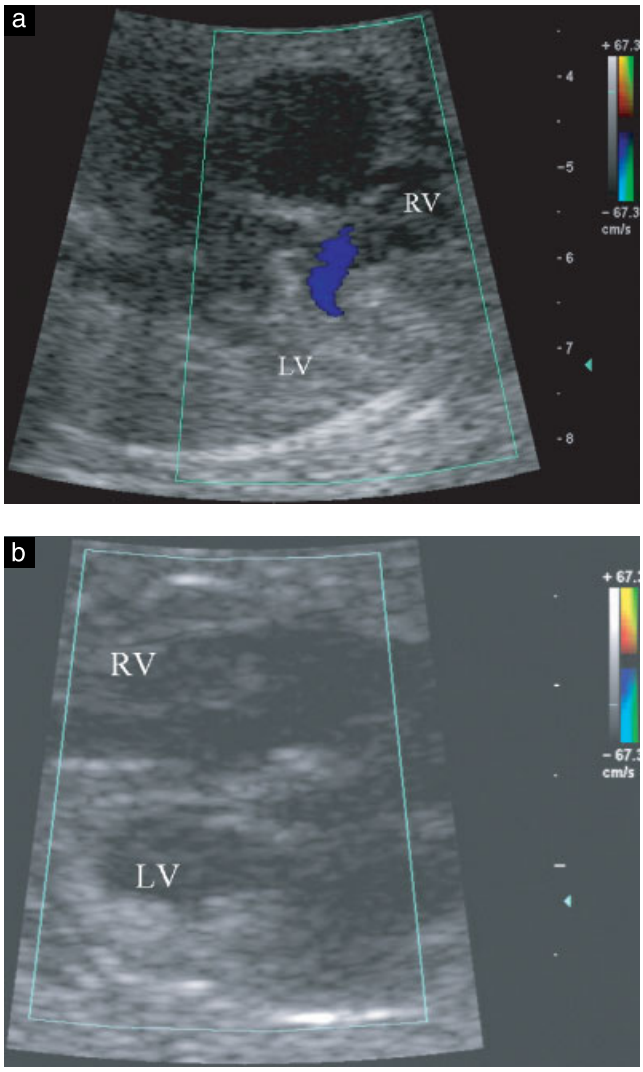

Figure 4 (a) Color Doppler ultrasound image showing small subaortic outlet defect, which did not close spontaneously. (b) Gray-scale four-chamber view of the same fetus. The subaortic ventricular septal defect is not visible in this mode. LV, left ventricle; RV, right ventricle.

by telephone until documented echocardiographic closure of the defect or until 1 year of age. Necropsies of 12 fetuses were performed at the University of Schleswig-Holstein, Campus Lübeck, by experienced pathologists trained in fetal autopsy. Statistical analysis was performed with the SPSS 11.0 package for Windows 2000 (SPSS, Chicago, IL, USA).

RESULTS

The mean gestational age at diagnosis of VSDs was 23.4 (range, 13–39) weeks.

Types of VSDs including all cases

One hundred and thirty-one (89.7%) of the fetuses had a muscular defect: 116 (79.5%) fetuses presented with a defect of the trabecular septum; 12 (8.2%) fetuses had a defect of the muscular outlet septum; and three (2.0%)

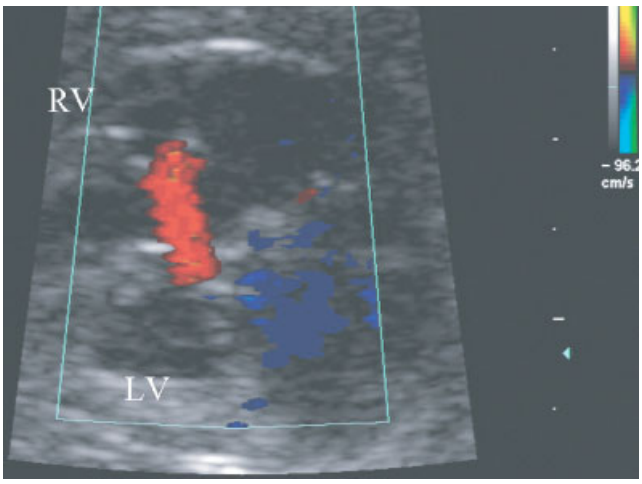

Figure 5 Color Doppler ultrasound image showing a small ventricular septal defect comprising the inlet part of the interventricular septum. This defect did not close spontaneously. LV, left ventricle; RV, right ventricle.

fetuses had a defect of the muscular inlet septum. Fifteen (10.3%) fetuses presented with a perimembranous defect.

Fetal karyotype by site of the VSD

Karyotyping was performed in 76 (52%) of 146 cases: 51 (67.1%) fetuses had a normal karyotype, and 25 (32.9%) cases with chromosomal anomalies were identified. Among those fetuses with aneuploidy there were five (20%) fetuses with trisomy 21, five (20%) with trisomy 13, and seven (28%) with trisomy 18. Four (16%) cases with triploidy were found. Two cases with Klinefelter-syndrome, one case with Turner-syndrome, and one case with a deletion of chromosome 13 were registered. Two (40%) of five fetuses with trisomy 21 presented with a perimembranous VSD and three (60%) of five had a muscular defect (three trabecular defects). In cases with trisomy 18, one (14.3%) of seven fetuses had a perimembranous defect and six (85.7%) had muscular defects. One of those fetuses had a defect of the muscular outlet septum and five fetuses had trabecular defects. Fetuses with trisomy 13 had muscular defects in all five (100%) cases. Four of those fetuses had a defect of the muscular outlet septum and one fetus had a trabecular defect. In cases with triploidy a muscular

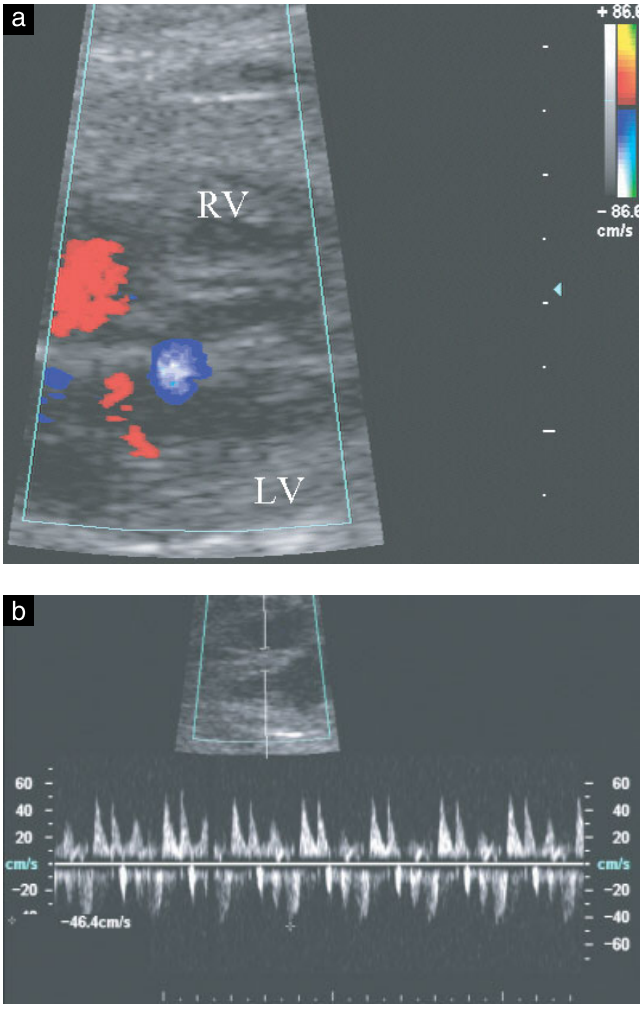

Figure 6 Color Doppler ultrasound images showing (a) small perimembranous septal defect and (b) the characteristic bidirectional flow pattern detected by spectral Doppler of the interventricular jet. LV, left ventricle; RV, right ventricle.

defect was detected in two (50%) of four fetuses and a perimembranous defect was seen in the other two (50%) fetuses (Table 1).

Outcome by site of the defect including all cases

There were 23 (15.8%) terminations of pregnancy and two (1.4%) stillbirths. One termination of pregnancy was carried out in a fetus with isolated VSD and normal

Table 1 Fetal karyotype and site of the defect in 76 cases of prenatally detected ventricular septal defects

	Fetal karyotype (n (%))					
Type of VSD	*Normal karyotype*	*Trisomy 21*	*Trisomy 13*	*Trisomy 18*	*Triploidy*	*Other*
Muscular	47 (61.8)	3 (3.9)	5 (6.6)	6 (7.9)	2 (2.6)	3 (3.9)
Trabecular	44 (57.9)	3 (3.9)	1 (1.3)	5 (6.6)	2 (2.6)	3 (3.9)
Outlet	3 (3.9)	—	4 (5.3)	1 (1.3)	—	—
Inlet	—	—	—	—	—	—
Perimembranous	4 (5.3)	2 (2.6)	—	1 (1.3)	2 (2.6)	1 (1.3)
Total (%)	51 (67.1)	5 (6.6)	5 (6.6)	7 (9.2)	4 (5.3)	4 (5.3)

VSD, ventricular septal defect.

Table 2 Outcome of fetuses with ventricular septal defects by site of the defect including all cases

	Fetal outcome (n *(%))*					
Type of VSD	*Alive after 1 year*	*Termination of pregnancy*	*Neonatal death*	*Stillbirth*	*NI after 1 year*	*VSD confirmed by necropsy*
Muscular	103 (70.5)	18 (12.3)	1 (0.7)	2 (1.4)	7 (4.8)	8 (5.5)
Trabecular	96 (65.7)	13 (8.9)	—	1 (0.7)	6 (4.1)	4 (2.7)
Outlet	5 (3.4)	4 (2.7)	1 (0.7)	1 (0.7)	1 (0.7)	3 (2.1)
Inlet	2 (1.4)	1 (0.7)		—	—	1 (0.7)
Perimembranous	10 (6.8)	5 (3.4)	—	—	—	4 (2.7)
Total (%)	113 (77.4)	23 (15.7)	1 (0.7)	2 (1.4)	7 (4.8)	12 (8.2)

NI, no information; VSD, ventricular septal defect.

karyotype because of severe non-cardiac malformations. There was an abnormal karyotype or severe extracardiac anomalies in all other cases which underwent termination of pregnancy (Table 2). One (0.9%) of 121 neonates died during the neonatal period due to prematurity and trisomy 18. One hundred and three (70.5%) neonates still alive after 1 year and with a complete dataset had a muscular type of VSD, of which 96 (65.7%) were trabecular, five (3.4%) affected the outlet septum and two (1.4%) the inlet septum. Ten (6.8%) neonates still alive after 1 year presented with a perimembranous defect. Postmortem examinations of 14 fetuses were performed. In all, eight (57.1%) muscular septal defects (four trabecular, three outlet defects, and one inlet defect) and four (28.6%) perimembranous defects were confirmed by the pathologist. In nine cases of termination of pregnancy the parents declined autopsy. In two cases of termination of pregnancy the cardiac defect could not be confirmed by autopsy due to the small size of the fetal heart and autolysis.

Outcome in 113 continuing pregnancies with neonatal follow-up to the age of 1 year

Closure rates by VSD site are given in Table 3. Thirty-seven (32.7%) of 113 defects closed spontaneously *in utero*, 50 (44.3%) defects closed spontaneously within 1 year and 26 (23%) defects did not close. Five (50%) of 10 perimembranous defects closed *in utero* and three (30%) of 10 perimembranous defects closed after 1 year. Twenty-nine (30.2%) of 96 muscular trabecular defects closed spontaneously *in utero* and 46 (47.9%) closed within the first postnatal year. Thus, the closure rate *in utero* and after 1 year for muscular and perimembranous defects were comparable. Two (40%) outlet defects did not close either during gestation or after the first year of postnatal life. There was no difference concerning the prenatal confirmation of the bidirectional flow pattern during pulsed-wave Doppler of the interventricular jet in defects that closed and those that did not close spontaneously.

Associated non-cardiac abnormalities

In 35 (23.9%) of 146 fetuses one or more extracardiac abnormalities were diagnosed, among them 18 (51.4%) fetuses with normal karyotype. Twelve (71%) of 17 aneuploid fetuses had combined abnormalities. The corresponding diagnosis postpartum or by autopsy and the gestational age at sonographic diagnosis are given in Tables 4 and 5.

Table 3 Closure of ventricular septal defects by site of the defect including continuing pregnancies with neonates alive after 1 year ($n = 113$)

	Closure of VSDs (n *(%))*			
Type of VSD	In utero	*After 1 year*	*No closure*	*Total*
Muscular	32 (31.1)	47 (45.6)	24 (23.3)	103 (91.2)
Trabecular	29 (30.2)	46 (47.9)	21 (21.9)	96 (85)
Outlet	3 (60)	—	2 (40)	5 (4.4)
Inlet	—	1 (50)	1 (50)	2 (1.8)
Perimembranous	5 (50)	3 (30)	2 (20)	10 (8.8)
Total (%)	37 (32.7)	50 (44.3)	26 (23)	113 (100)

VSD, ventricular septal defect.

DISCUSSION

VSD represents a minor anomaly of the four-chamber view and its intrauterine detection rate is therefore low[17]. In contrast to large muscular septal defects, which can be diagnosed in the four-chamber view, the detection of perimembranous subaortic defects can only be achieved by visualization of the modified four-chamber view and long-axis view of the left ventricle. Color Doppler echocardiography is mandatory for the diagnosis of small ventricular defects that cannot be diagnosed by B-mode ultrasonography. During intrauterine life there is no pressure gradient between left and right ventricles due to the physiological patency of the ductus arteriosus and the foramen ovale. Thus, the prenatal diagnosis of small muscular VSDs is difficult, although detection of shunting is possible albeit dependent on a good color-operating setting and the visualization of all parts of the interventricular septum. Small VSDs demonstrate characteristic bidirectional flow pattern[13] and all of them were confirmed in our study by spectral Doppler analysis of the interventricular jet. In contrast, in newborns with

Table 4 Extracardiac abnormalities in euploid fetuses with an isolated ventricular septal defect

Gestational age at examination (weeks)	*Prenatal diagnosis*	*Diagnosis postpartum/autopsy*
15	+	Hydrops fetalis
18	+	Club feet
16	+	Hydronephrosis
	+	Omphalocele
	+	Facial cleft
	+	Encephalocele
21	+	Omphalocele
21	+	Single umbilical artery
21	+	Facial cleft
	−	Orbital hypoplasia
	+	Congenital diaphragmatic hernia
	+	Pulmonary hypoplasia
	−	Shortened digit iv
21	−	Inguinal hernia
22	−	Epidermolysis bullosa
23	+	Choroid plexus cysts
24	+	Omphalocele
24	+	Hydrops fetalis
25	+	Hydrocephalus
27	+	Encephalocele
29	+	Tuberous sclerosis
	+	Omphalocele
30	+	Thoracic myelomeningocele
	+	Hydrocephalus
	+	Arnold Chiari malformation, Type II
	+	Club feet
32	+	Hydronephrosis
34	+	Placental cysts
		Single umbilical artery
37	+	Hydronephrosis

Table 5 Extracardiac abnormalities in aneuploid fetuses with an isolated ventricular septal defect

Karyotype	*Gestational age at examination (weeks)*	*Prenatal diagnosis*	*Diagnosis post-partum/autopsy*
47,XXY	17	+	Hydrocephalus internus
		+	Fixed extended fingers
		+	Single umbilical artery
		+	Echogenic bowl
del(13)(q3.1)	30	+	Holoprosencephaly
		+	Club feet
Trisomy 13	21	+	Brachycephaly
		+	Holoprosencephaly
		+	Flat profile
		+	Omphalocele
Trisomy 13	14	+	Facial cleft
		+	Craniofacial dysplasia
		+	Hexadactyly
		+	Lobar holoprosen-cephaly
Trisomy 13	14	+	Hexadactyly
		+	Facial dysmorphia
Trisomy 13	31	+	Facial cleft
		+	IUGR
Trisomy 18	15	+	Micrognathia
		+	Congenital diaphrag-matic hernia
		+	Omphalocele
Trisomy 18	21	+	Single umbilical artery
		+	Choroid plexus cysts
		+	Clenched fingers
		+	Omphalocele
Trisomy 18	28	+	Hydronephrosis
		+	Cleft palate
		+	Joint contractures
		+	Omphalocele
		+	IUGR
Trisomy 18	13	+	Facial cleft
			Omphalocele
Trisomy 21	13	+	Cystic hygroma
Trisomy 21	39	−	Anal atresia
Trisomy 21	17	+	Brachycephaly
Triploidy	16	+	Single umbilical artery
		+	Short femur
Triploidy	17	−	Syndactyly
		+	Cystic hygroma
Triploidy	18	−	Micrognathia
		−	Horseshoe kidney
		+	Facial dysmorphia
Turner syndrome	18	+	Hydrops fetalis

IUGR, intrauterine growth restriction.

muscular septal defects there is usually a high-velocity shunt due to the pressure gradient between the left and right ventricles, which can be seen by color Doppler echocardiography.

The distribution of the different types of VSDs in our study partially differs from that of pediatric studies in the literature. In pediatric series in which the children were followed up from birth, muscular septal defects were more common than perimembranous defects, similar to our results[15]. In other studies, the incidence of perimembranous defects was higher than that of muscular defects[9]. Different study populations (prenatal vs. postnatal) and criteria of diagnosis and methods of echocardiography might account for these variations.

Whenever fetal echocardiography reveals a VSD, a complete sequential analysis of the fetal heart is mandatory[1,2,18,19]. Extracardiac anomalies associated with a VSD include chromosomal abnormalities (e.g. trisomy 21, 13, 18) in up to 40% in some series[1,2,20].

It is unlikely that the 32.9% association of VSD and abnormal karyotype in our study is representative. The study population was a selected group from a referral center. Many cases were referred due to existing extracardiac abnormalities, including chromosomal anomalies, and diagnosis of VSDs in aneuploid fetuses with associated anomalies is easier. In accordance with Paladini *et al.* our report reveals a high proportion of euploid fetuses with an isolated VSD and extracardiac anomalies. Again, in many cases the detection of extracardiac anomalies probably preceeded the detection of a VSD and was the indication for referral.

We demonstrated that VSDs can undergo spontaneous closure *in utero* and after birth, and that the closure rate depends on the type of VSD diagnosed. In our series,

VSDs closed in 44.3% of newborns still alive after 1 year. In this population of neonates the intrauterine closure rate of muscular VSDs was 31.1%, with that of perimembranous defects 50%. Paladini *et al.*[9] reported an even higher *in utero* closure rate of perimembranous defects compared to our data. However, they only found a 16.7% intrauterine closure rate of muscular defects in a group of 40 continuing pregnancies. In essence, our report confirms the previous results of Paladini *et al.* of high intrauterine closure rates for very small perimembranous and outlet defects. Slightly different results in terms of closure rates might be in part due to the differential classification of VSDs. Furthermore, difficulties in locating and thus correctly diagnosing septal defects may also account for some of the discrepant results. The finding of Paladini *et al.* that smaller defects close more often than larger defects seems logical, but one has to consider that the exact measurement of VSDs in sizes smaller than 3 mm, as reported by Paladini *et al.*, is hampered by technical difficulties and thus may lack reproducibility[9]. Pediatric results reporting a higher spontaneous postpartum closure rate of muscular septal defects compared to perimembranous defects underline the possibility of spontaneous closure of VSDs[21].

There are two methodological limitations of our study. Firstly, it is a retrospective review of all cases with an isolated VSD diagnosed prenatally. In our ultrasound unit fetal echocardiography is mandatory in cases with fetal aneuploidy. Consequently, the incidence of abnormal karyotypes in fetuses with VSDs in our report is high. Secondly, as mentioned above, the different types of VSDs have different detection rates, with muscular septal defects being more easily detected in the classical four-chamber view compared to perimembranous defects and isolated subarterial outlet VSDs, whose diagnosis require the examination of the ventricular outflow tracts and a long-axis view of the left ventricle. The difference between prenatal and postnatal findings can be accounted for by the increased rate of spontaneous fetal loss in cases with chromosomal defects. Finally, in view of the difficult diagnosis, we must consider the possibility of a false-positive diagnosis of a VSD and its apparent intrauterine closure.

New echocardiographic views like the 'in-plane' view of the interventricular septum as described by Paladini *et al.*[18] may improve the assessment of the interventricular septum and provide additional information in cases of a suspected VSD. However, the visualization rates are strongly dependent upon fetal position and can range between 0–100%. Yagel *et al.*[22] have recently reported on the detailed assessment of a fetal VSD with 4D color Doppler ultrasound using spatio-temporal image correlation technology. This technique allows measurement of the area of the defect, its spatial location in the septum and its correlation with the cardiac cycle.

The results presented in this study may be helpful for the prenatal counseling of parents. Firstly, the presence of VSDs increases the risk of aneuploidy of the affected fetus and fetal karyotyping should be offered. Secondly, a careful search for extracardiac-associated anomalies should be performed. Thirdly, roughly 33% of small VSDs only detectable by color Doppler imaging in fetuses with normal karyotype are likely to close spontaneously during pregnancy, with a further third closing within the first year postnatally, implying that only a minority of such small VSDs will require surgical repair.

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