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Isolated ventricular septal defects in the era of advanced fetal echocardiography: risk of chromosomal anomalies and spontaneous closure rate from diagnosis to age of 1 year

O. GÓMEZ*, J. M. MARTÍNEZ*, A. OLIVELLA*, M. BENNASAR*, F. CRISPI*, N. MASOLLER*, J. BARTRONS†, B. PUERTO* and E. GRATACÓS*

**Fetal Cardiology Unit, Department of Maternal–Fetal Medicine, ICGON, Hospital Clínic, University of Barcelona and Centre for Biomedical Research on Rare Diseases (CIBERER), Barcelona, Spain; †Pediatric Cardiology, Hospital Sant Joan de Déu, Barcelona, Spain*

KEYWORDS: congenital heart defect; fetal echocardiography; isolated; karyotype; outcome; spontaneous closure; ventricular septal defect

ABSTRACT

Objectives *To evaluate, in a cohort of 248 fetuses seen at a tertiary referral center, the frequency of isolated ventricular septal defects (VSD) among all congenital heart defects (CHD), the association with chromosomal and postnatal anomalies and the rate of spontaneous closure.*

Methods *This was a 6-year study on 10 800 women referred for fetal echocardiography, with 995 confirmed cases of CHD. The prevalence and characteristics of VSDs were analyzed, including follow-up until 1 year of age. Multivariate binary logistic regression analysis was performed to test the independent contribution of the ratio of the diameter of the VSD to that of the aorta (VSD/aorta ratio) (< 0.5 or ≥ 0.5) and location of VSD (perimembranous or muscular) in the prediction of spontaneous closure before the age of 1 year.*

Results *Two hundred and forty-eight VSDs (24.9% of all CHDs) were diagnosed, of which 216 (87.1%) were muscular and 32 (12.9%) perimembranous. Median gestational age at diagnosis was 30.4 (range, 17–41) weeks and mean size 2.6 ± 0.77 mm. Clinically relevant chromosomal anomalies were found in one (3.1%) perimembranous VSD compared with none in 216 muscular defects ($P = 0.12$). Postnatal malformations were diagnosed in eight of the 211 cases (3.8%) evaluated at 12 months postpartum. Spontaneous closure occurred prenatally in 13 fetuses (5.2%) and postnatally in 151 of the 198 infants (76.3%) who had an open VSD at birth. Closure was predicted by the VSD/aorta ratio (odds ratio (OR) 0.445 (95% CI, 0.216–0.914);* $P < 0.03$*) and location (OR 0.385 (95% CI, 0.160–0.926);* $P < 0.03$*).*

Conclusions *In our fetal cardiology unit, isolated muscular VSD is today the most prevalent CHD. In contrast to the findings of postnatal studies, muscular VSDs were more common than perimembranous VSDs. Perimembranous VSDs were associated with a higher risk of chromosomal anomalies than were muscular VSDs, which had a similar risk to those of normal pregnancies. Spontaneous closure of the VSD was frequent and occurred in most cases postnatally.* *Copyright © 2013 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Ventricular septal defect (VSD) is the most common congenital heart defect (CHD) in newborns, affecting 25–30% of neonates with cardiac defects[1]. According to recent systematic reviews, the finding of VSD at birth has increased substantially when compared with the results of older studies, probably because of changes in screening and diagnostic methods[2,3]. In the same vein, recent technical advances in fetal echocardiography have greatly improved the prenatal detection of VSDs, especially of those small defects that frequently appear as an isolated finding. However, the prevalence and distribution of the different types of fetal VSD are not well known, and further studies are required to determine better the risk of postnatal and chromosomal anomalies associated with this CHD when diagnosed prenatally.

It is generally accepted that the prognosis of isolated VSD in the postnatal period is good, with a high rate of

Correspondence to: Dr O. Gómez del Rincón, Fetal Cardiology Unit, Department of Maternal Fetal Medicine, Institut Clinic de Ginecologia, Obstetricia i Neonatologia, Hospital Clínic, c/ Sabino de Arana 1, 08028 Barcelona, Spain (e-mail: ogomez@clinic.ub.es)

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spontaneous closure during the first years of life. However, the evolution and outcome of prenatally isolated VSDs have not been well established, since only a few studies have evaluated this type of CHD when diagnosed in fetal life[4–6]. Extracardiac anomalies associated with VSDs include chromosomal anomalies in 26–32% of cases according to two recent large studies[4,5]. This rate is significantly higher than expected from postnatal series[7], which in all probability is due to differences in the spectrum of prenatally diagnosed patients, with a high proportion of extracardiac malformations associated with VSDs. There is also scant information on the perinatal evolution of fetal VSDs regarding the rate of spontaneous closure during fetal life or up to the age of 1 year[4–6]. As previously mentioned, caution should be taken with these data and larger studies are required to provide more precise information on the evolution of VSDs during fetal and early postnatal periods.

In this study we report on a large cohort of prenatally diagnosed isolated VSDs, describing the prevalence of different types of VSD with regard to the location in the septum, the risk of associated postnatal and chromosomal anomalies and the frequency of spontaneous closure of the VSD throughout gestation and during the first postnatal year.

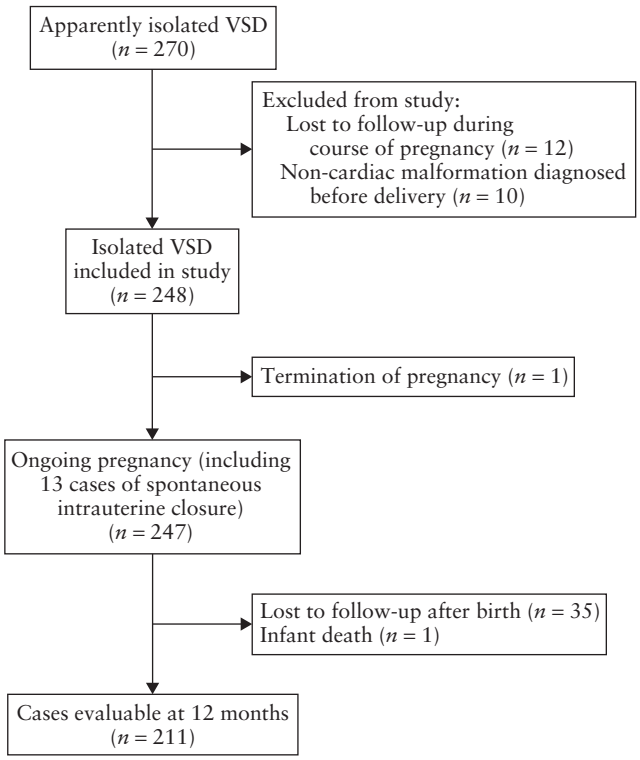

Figure 1 Flowchart of the 248 cases included in the study.

METHODS

This was a cohort study on a consecutive series of isolated VSDs from a total of 10 800 echocardiographic scans carried out in our fetal cardiology unit, which operates as a referral center for pregnancies at high risk for CHD, from January 2005 to August 2011. The sole inclusion criterion was diagnosis of an apparently isolated VSD, thus those defects associated with other structural anomalies at the time of diagnosis, i.e. other CHD, vascular anomalies and/or non-cardiac malformations, were excluded from the study. We found 995 cases of fetal CHD, of which 270 were isolated VSD. Not all cases with known chromosomal anomalies are routinely referred for fetal echocardiography in our unit, but only those patients who decide to continue with the pregnancy. As a main objective of our study was to determine the risk of aneuploidy after the diagnosis of an isolated VSD in a population of pregnant women referred for echocardiography, we did not include the group of known cases of chromosomal abnormality in the analysis. From the original cohort of 270 isolated VSDs, 10 cases (3.7%) were excluded later because of the subsequent diagnosis of an extracardiac structural malformation before delivery, and 12 cases (4.4%) were lost to follow-up during the course of the pregnancy (Figure 1). In the remaining 248 cases, the following data were obtained from our computerized fetal CHD database: indication for fetal echocardiography, gestational age at diagnosis, size and location of the defect, diameter of the aortic root, Doppler demonstration of flow across the defect, presence of chromosomal anomalies, intrauterine closure, pregnancy outcome and neonatal follow-up until the age of 12 months. The study protocol was approved by the local ethics committee, and all patients provided oral consent for the use of the images for clinical studies.

Ultrasound scans were performed by obstetricians experienced in evaluating the fetal heart. Gestational age was determined by ultrasound measurement of the crown–rump length between 11 and 14 weeks[8] or the biparietal diameter between 14 and 22 weeks[9]. All patients underwent a detailed fetal echocardiographic examination, which includes standard planes with color Doppler assessment, obtained following guidelines of the International Society of Ultrasound in Obstetrics and Gynecology and other expert guidelines[10–12]. Whenever a VSD was suspected, the septum was further studied with color Doppler ultrasound in at least two different planes in order to confirm the defect. Since the pressure gradient across a VSD is small during fetal life, the color-flow velocity scale was reduced to identify better low-velocity jets across the defect. We also confirmed any flow across the septum by pulsed-wave Doppler study. Special care was taken to ensure that the ultrasound beam was perpendicular to the septum, so that the flow across the defect could be defined more accurately.

The type of VSD was classified according to its location as perimembranous or muscular[7,13]. Perimembranous VSDs were subdivided into inlet and outlet subtypes, depending on whether the defect was located in the lower or upper portion of the membranous septum, and muscular VSDs into mid-muscular VSDs (superior to the moderator band) and apical VSDs (inferior to the moderator band). We chose this classification because it

has been used previously for this purpose, although it may appear to be an oversimplification from the point of view of the pediatric cardiologist or surgeon[4]. It is important to note that perimembranous VSDs can also open to the trabecular part of the septum, and muscular defects can also be classified as 'inlet type' or 'outlet type', including some malaligned defects. These aspects are very important when planning postnatal treatment but are difficult to identify prenatally. The size of the defect was determined at the point of maximum diameter by gray-scale ultrasound in large and well defined defects and by color Doppler ultrasound in small, tortuous and/or multiple defects, which comprised the vast proportion of cases in this study. To estimate the size of the defect, we routinely evaluated whether it showed posterior or anterior extension on the four-chamber view, which was of great help in defining the path of the defect and in choosing the point of maximum diameter to make the measurement. Cine-loop function was particularly helpful in assessing the relationship of the defect to other cardiac structures and in establishing its size. In all cases, several images were recorded on videotape for later re-evaluation if necessary and, in examinations performed after September 2006, spatiotemporal image correlation (STIC) volumes with color Doppler were also obtained ($n = 60$). In order to negate the influence of fetal weight and gestational age on absolute VSD size, the ratio of the diameter of the VSD to that of the aorta (VSD/aorta ratio) was calculated in all cases. For this, the internal diameter of the aortic root during systole was measured at the level of the valve.

An invasive procedure was offered in all cases in which the karyotype was unknown at the time of diagnosis. A 4–6-weekly follow-up until delivery was also scheduled to evaluate the evolution of the defect throughout gestation. The reliability of the VSD diagnosis was assessed by postnatal examination by a pediatric cardiologist or by autopsy in cases of termination of pregnancy or postnatal death. As shown in Figure 1, 35 cases were lost to follow-up after birth and there was one infant death. In the remaining 211 children (85.4% of ongoing pregnancies) we obtained complete information at 1 year of age. Multivariate binary logistic regression analysis was performed to test the independent contribution of VSD/aorta ratio (< 0.5 or ≥ 0.5) and location of the defect (perimembranous or muscular) in the prediction of spontaneous closure from diagnosis to 12 months of age. Statistical analysis was performed with the SPSS v. 17.1 for Windows Statistical Package (SPSS, Chicago, IL, USA).

RESULTS

During the 6-year study period, 248 isolated VSDs were diagnosed among 995 CHDs (24.9%). The median gestational age at diagnosis was 30.4 (range, 17–41) weeks. One hundred and seventy-six cases (71.0%) were diagnosed in the third trimester. Indications for performing echocardiography were: suspicion of CHD in 215 cases (86.7%), increased nuchal translucency in 10 (4.0%), fetal growth restriction in nine (3.6%), maternal diabetes in five (2.0%), abnormal cardiac rhythm in five (2.0%) and CHD in a previous pregnancy in four (1.6%).

Two hundred and sixteen (87.1%) fetuses had a muscular VSD (Figures 2 and 3) and 32 (12.9%) a perimembranous defect (Figures 4 and 5). The mean size of the defect at diagnosis was 2.6 ± 0.77 mm. The distribution according to location and VSD/aortic ratio is shown in Table 1. Only 1 (0.4%) malalignment defect was detected, corresponding to 3.1% of the perimembranous VSDs. Flow across the defect was clearly identified by color Doppler in 238 (96.0%) cases, while in 10 perimembranous defects (all smaller than 2 mm) the defect could be demonstrated only by pulsed Doppler.

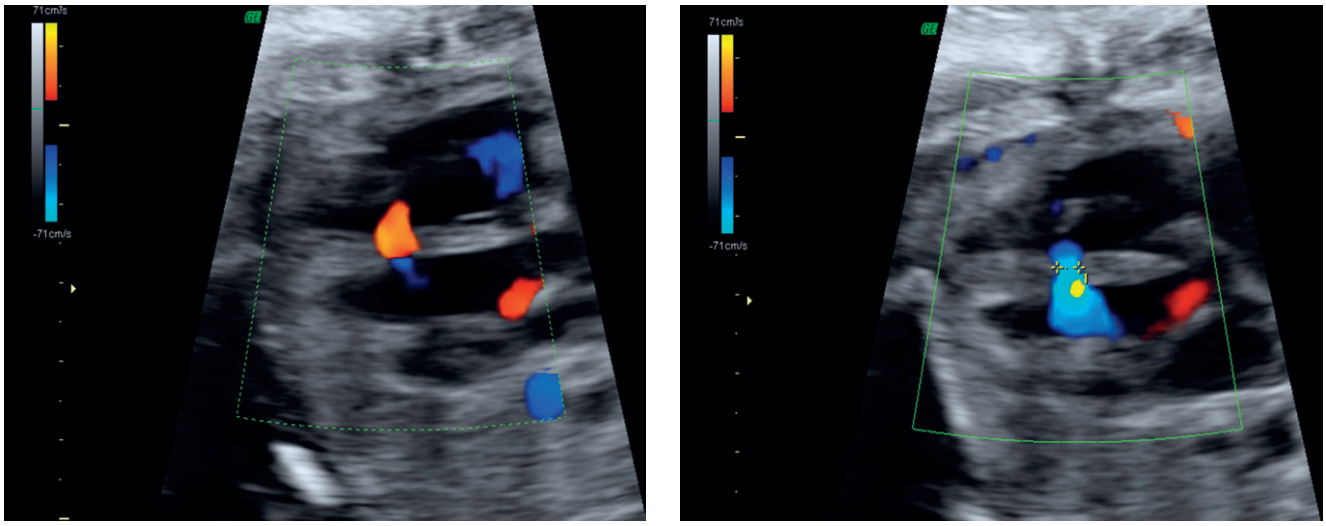

Figure 2 Color Doppler images of ventricular septal defects located in mid-muscular septum, showing bidirectional flow across defect. Note that size of defect may vary slightly between systole and diastole; in the present study the greater diameter was always chosen to evaluate the size of the defect.

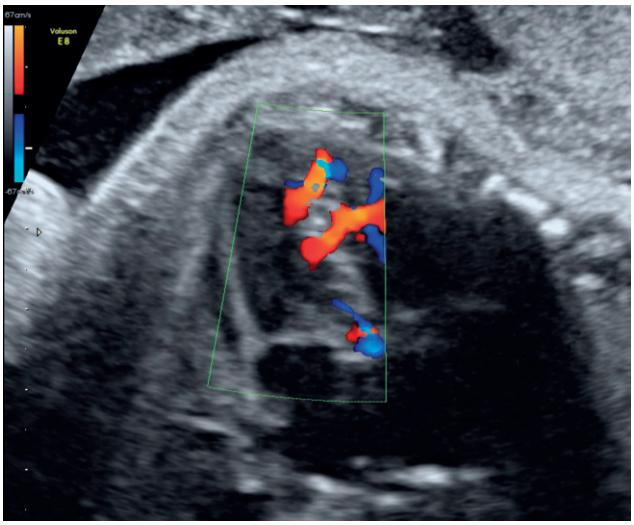

Figure 3 Color Doppler image of a double apical ventricular septal defect in portion of muscular septum located below the moderator band.

Amniocentesis for genetic diagnosis was performed in 119 (48.0%) pregnancies and in the remaining 129 cases (52.0%) the karyotype was clinically assessed postnatally. The prevalence of chromosomal anomalies was 1.2% (3/248 cases). Table 2 summarizes the information on different types of chromosomal anomalies as well as clinical and ultrasound data. Importantly, only one of the three cases had a chromosomal anomaly with clinical significance, corresponding to a microdeletion in the critical region of chromosome 22 for DiGeorge syndrome in a fetus with a perimembranous VSD of 4.5 mm. As shown in Table 2, in the other two cases with non-clinically relevant chromosomal alterations, mid-muscular VSDs were diagnosed. In summary, only one of the 32 perimembranous VSDs (3.1%) compared to none of the 216 muscular defects, was associated with chromosomal abnormalities of clinical significance ($P = 0.12$; Fisher's exact test).

There was only one termination of pregnancy in our series (Figure 1), in a case of early premature rupture of membranes associated with anhydramnios. A perimembranous VSD was confirmed in the fetus at autopsy. The mean gestational age and the birth weight at delivery of the remaining ongoing pregnancies were 39.4 (range, 31.1–42.3) weeks and 3278 (range, 1530–5000) g, respectively. In eight of the 211 cases available for evaluation at 12 months of age (3.8%) a congenital defect was diagnosed after birth: five minor cardiac defects (mild tricuspid stenosis, mild pulmonary stenosis and three cases of ostium secundum atrial defect), one case of aortic coarctation that needed surgery, and extracardiac malformations in the other two cases (one case of hypospadias and one of mild hydronephrosis). Karyotype was normal in all eight cases. Sudden death occurred in an otherwise clinically healthy infant at 7 months of age.

Closure of the defect during fetal life could be demonstrated in 13 of the 247 ongoing pregnancies (5.3%). During the postnatal period, 35 cases (14.2%) were lost to follow-up. In 151 of the remaining 198 cases born with a VSD (76.3%) the VSD closed spontaneously before the age of 12 months (24 of them in the early neonatal period before postnatal echocardiography had been performed). Seven of the 198 children (3.5%) needed cardiac surgery before 12 months and 40 (20.2%) still had an open defect at 12 months. The model including the VSD/aorta ratio and location of the VSD to predict spontaneous closure of the defect explained 8% of the uncertainty (Nagelkerke R^2). The location of the defect in the muscular portion of the septum (odds ratio (OR) 0.385 (95% CI, 0.160–0.926); $P = 0.03$) as well as the VSD/aorta ratio (OR 0.445 (95% CI, 0.216–0.914); $P = 0.03$) significantly predicted the

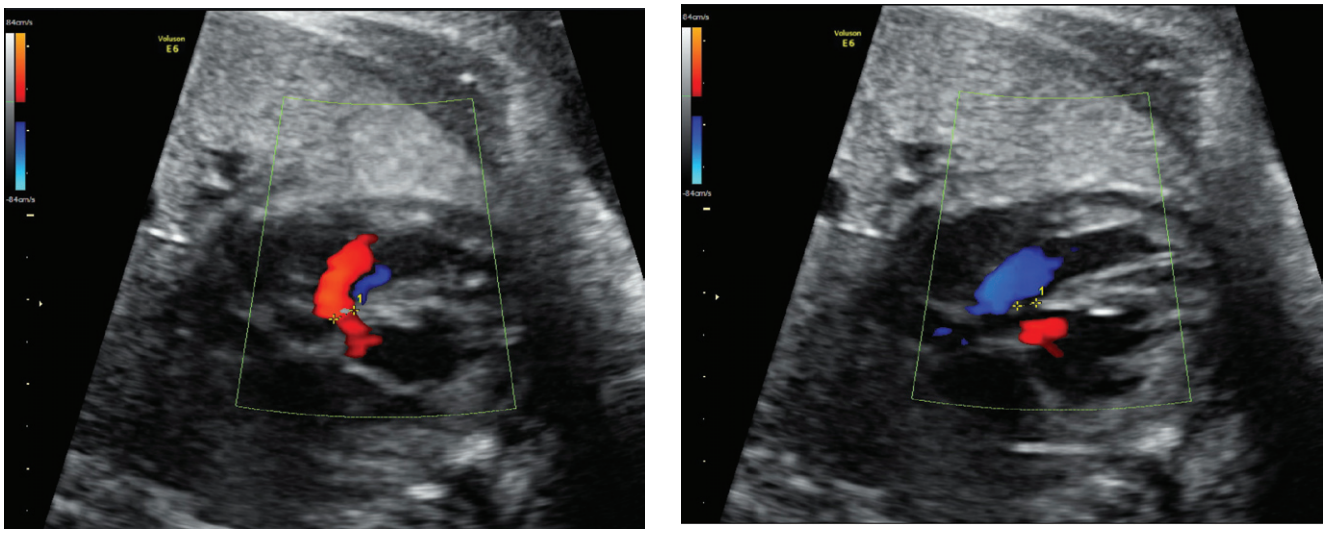

Figure 4 Color Doppler images of inlet perimembranous ventricular septal defect, situated in lower portion of perimembranous septum. Flow across defect (red) clearly presents a different direction from that of aorta (blue), which comes entirely from left ventricle.

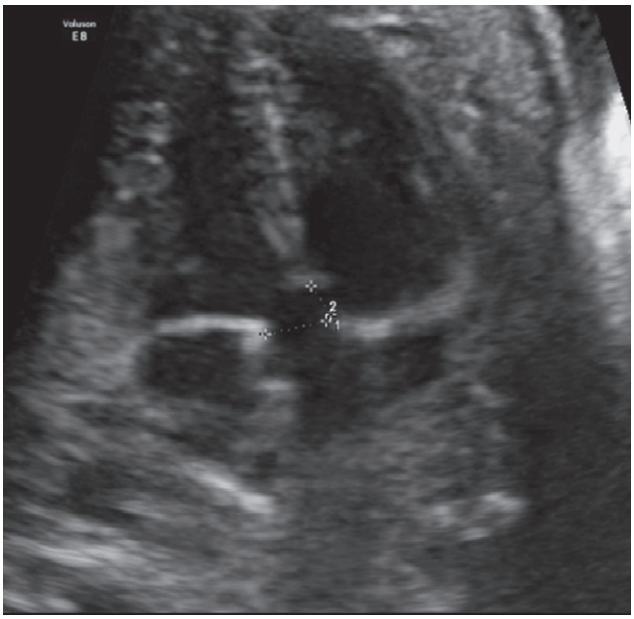

Figure 5 Ultrasound image of outlet perimembranous ventricular septal defect in systole, located in upper portion of membranous septum. Anterior wall of aorta is correctly aligned with defect and aortic valve is entirely connected to left ventricle.

Table 1 Types of ventricular septal defect (VSD) in relation to location and ratio of diameter of VSD to diameter of aorta (VSD/aorta ratio)

	VSD/aorta ratio		
Type of VSD	*< 0.5*	*≥ 0.5*	*Total*
Inlet perimembranous	8 (3.2)	8 (3.2)	16 (6.5)
Outlet perimembranous	2 (0.8)	14 (5.6)	16 (6.5)
Mid muscular	70 (28.2)	80 (32.3)	150 (60.5)
Apical muscular	30 (12.1)	36 (14.5)	66 (26.6)
Total	110 (44.4)	138 (55.6)	248 (100.0)

Data given as *n* (%).

occurrence of spontaneous closure of the defect. The rate of spontaneous closure at different stages (intrauterine life, early and late postnatal periods), as well as the proportion of cases requiring surgery before the age of 12 months in relation to VSD type and VSD/aorta ratio are summarized in Table 3. Briefly, spontaneous intrauterine closure occurred more frequently in perimembranous VSDs with small defects while spontaneous closure in the postnatal stage happened mainly in newborns with small muscular defects.

DISCUSSION

This study is, to our knowledge, the largest series of apparently isolated prenatally detected VSDs, including a large cohort of newborns with complete follow-up at the age of 12 months. In general, prenatally isolated muscular VSDs were about seven times more prevalent than perimembranous ones and were associated with a good outcome, with no case having chromosomal anomalies of clinical significance and a 1–2% risk of needing surgery during the first year of postnatal life. On the other hand, perimembranous VSDs were associated with a 3.1% risk of chromosomal anomaly, and if the VSD/aorta ratio was above 0.5, the probability of requiring surgery in the first year was at least 50%. These data may be of help in counseling patients about prenatally detected isolated VSDs.

Our study confirms that, as in postnatal life, isolated VSD is a frequent CHD during fetal life[2,3]. The detection of VSDs before birth has greatly increased over the last few years owing to the use of higher-quality equipment and the incorporation of expert guidelines for the screening of CHD during pregnancy[2]. As shown in Table 1, 44.4% of VSDs had a VSD/aorta ratio of less than 0.5, 71% of cases were diagnosed in the third trimester and 87% of the VSDs were suspected on ultrasound screening in our series, which is routinely performed at 11–14, 19–22 and 32–34 weeks' gestation at our institution. A noteworthy finding of this study is that the distribution of type of isolated VSD during fetal life differs significantly from that found postnatally[14]. Thus, while pediatric series have classically reported that perimembranous defects account for approximately 75% of total VSDs, small mid-muscular VSDs represented the vast majority of cases diagnosed in the prenatal period. The difference is likely to reflect the high rate of spontaneous resolution, possibly combined with some degree of under-ascertainment due to the common absence of clinical signs in muscular defects[15].

The rate of chromosomal anomalies associated with isolated fetal VSD has not been well established to date, as previous studies did not stratify the risk for isolated *vs* non-isolated VSDs. Indeed, the two most recent large studies found a rate of 26–32% of chromosomal anomalies[4,5], which is significantly higher than expected from postnatal series[14], but these series included cases with extracardiac anomalies and associated known chromosomal anomalies. On the other hand, in the only study on fetuses with isolated VSD diagnosed by color Doppler ($n = 16$), the risk of chromosomal anomalies was significantly lower[6]. In that study one of the fetuses had trisomy 21, indicating a prevalence of this aneuploidy of 6.2%. However, it is important to note that the fetus also had an increased nuchal translucency on the first-trimester scan and the indication for performing echocardiography was the abnormal karyotype. In another study, isolated fetal VSDs were associated with chromosomal anomalies in more than 10% of cases, but they were not differentiated by type of defect[16]. The rate of chromosomal abnormalities in this prospective series was much lower than previously reported[4–6,16]. Only one of the 32 perimembranous VSDs was associated with a clinically significant chromosomal anomaly. Therefore, since none of the 216 isolated muscular VSDs was associated with a chromosomal anomaly of clinical significance, we suggest that muscular defects, whenever they remain isolated throughout pregnancy, may be

Table 2 Description of cases of ventricular septal defect (VSD) with chromosomal anomalies

Karyotype	*GA at diagnosis (weeks)*	*Type of VSD*	*Size (mm)*	*Postnatal malformation*
46,XX, ish del (22) (q11.2q11.2) (TUPLE1-)*	33.3	Outlet perimembranous	4.5	No
46,XY, inv (7) (q11q22) pat	23.0	Mid muscular	2.0	No
45,XX, der (13;14) (q10;q10) dn	36.1	Mid muscular	3.0	No

*Chromosomal anomaly with clinical relevance. GA, gestational age.

Table 3 Rate of spontaneous closure of ventricular septal defects (VSD) at different stages according to type and ratio of diameter of VSD to diameter of aorta (VSD/aorta ratio)

	Spontaneous closure					
Type of VSD	*Intrauterine*	*Postpartum*	*Before 12 months*	*Surgery before 12 months*	*VSD open at 12 months*	*Total*
Perimembranous						26 (12.3)
VSD/aorta ratio < 0.5	8 (3.8)	3 (1.4)	2 (0.9)	—	6 (2.8)	
VSD/aorta ratio ≥ 0.5	1 (0.5)	1 (0.5)	—	4 (1.9)	1 (0.5)	
Muscular						185 (87.7)
VSD/aorta ratio < 0.5	2 (0.9)	8 (3.8)	65 (30.8)	—	12 (5.7)	
VSD/aorta ratio ≥ 0.5	2 (0.9)	12 (5.7)	60 (28.4)	3 (1.4)	21 (10.0)	
Total	13 (6.2)	24 (11.4)	127 (60.2)	7 (3.3)	40 (19.0)	211 (100.0)

Data given as *n* (%).

considered defects with a low risk of chromosomal anomalies.

We have shown that the false-negative rate for the prenatal detection of extracardiac malformations associated with VSDs is low, since only 8 of 211 (3.8%) of the neonates presented with unexpected malformations, the majority of them non-serious and considered as not identifiable or difficult to identify during pregnancy. All these children had a normal karyotype.

With respect to spontaneous closure of prenatally diagnosed isolated VSDs, we found 5% of cases closing prenatally and 76% closing before the age of 1 year. As illustrated in Table 3, prenatal closure occurred mainly in the group of small perimembranous defects, while postnatal closure was found mainly in the group of muscular VSDs. Additionally, in 16% of postnatal closures, the defect closed in the peripartum or in the early neonatal period. We ruled out a false-positive diagnosis of VSD in all these cases by reassessing the two-dimensional ultrasound scans and the STIC volume videos in three cases with a diagnosis of perimembranous VSD. Moreover, the presence of flow across the defects by color and/or pulsed-wave Doppler study was a requirement for inclusion in this study. It is well known that a proportion of VSDs undergo spontaneous closure within the first 2 years of life by different mechanisms[17–20]. Defects in the muscular septum are supposed to close as a result of growth and hypertrophy of the surrounding muscular septum, whereas small membranous defects can close by formation of a tricuspid valve aneurysm or prolapse of the right aortic cusp[21]. Although it has also been demonstrated that VSDs can undergo spontaneous closure during fetal life[4–6], the mechanisms involved have not been prospectively evaluated in the fetus. Our results show a similar rate of postnatal closure as previously reported[17–19] but a lower number of prenatal closures[4–6]. It is important to note that although prenatal spontaneous closure occurred basically in the group of small perimembranous VSDs in our series, we did not evaluate prospectively the role of tricuspid valve tissue formation as a mechanism for spontaneous closure in this group of defects.

We acknowledge that our study has several limitations. First, we used a simplified classification of VSDs. Second, determining the size of septal defects is not always easy on gray-scale ultrasound, since some defects may present with a tortuous path or may be multiple. Moreover, small defects are only visible on color Doppler, which can falsely overestimate the size of the defect. Therefore, results reported in relation to the size of the defect should be interpreted with caution, and future studies are required to evaluate the potential utility of methodologies such as STIC in the three-dimensional evaluation of the extent and area of VSDs. Third, the incidence of small muscular defects that were noticed in late pregnancy is high in our series. This probably reflects a bias due to a high level of local skills at cardiac scanning and the use of third-trimester ultrasound, both of which may not necessary apply to other clinical settings. However, the number of perimembranous defects detected was small, which prevents our drawing firm conclusions regarding the risk of associated chromosomal anomalies and outcomes. Fourth, the policy for closure of VSDs varies between pediatric cardiac surgical units, so again the results regarding spontaneous closure may not be widely applicable. Finally, 13.4% of the ongoing pregnancies were lost during postnatal follow-up. We recognize that this percentage is rather high, and may limit the validity of some of the conclusions of the study.

To summarize, our study contains the largest cohort of prenatally detected cases of isolated VSD and newborns with complete follow-up at 12 months of age. In the setting of a fetal cardiology unit, isolated VSD represents the most common cardiac defect. Muscular defects are

seven times more frequent than perimembranous ones in fetal life, which represents a reversal of the situation found in pediatric series. The diagnosis of an isolated muscular VSD can be considered a benign finding, with a similar risk of associated chromosomal anomalies to that of a normal pregnancy. However, further information is needed to establish the risk of chromosomal anomalies associated with perimembranous defects. The diagnosis of 'isolated' VSD can be considered reliable in the large majority of cases and the rate of postnatally detected malformations is low. The vast majority of muscular VSDs will spontaneously close before the age of 1 year. We hope that the information reported here will be of help for counseling, and in the management of prenatally diagnosed isolated VSD.

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